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PHYSIOLOGICAL RESPONSES OF TRANSPLANTED PROSTATIC TISSUE IN THE ANTERIOR CHAMBER OF THE EYES OF RABBITS[1]

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OF the many experimental methods used for the study of autotransplantation of tissue, the anterior chamber of the eye as a situs has been found to be of particular value to observe the physiological and anatomical changes. The earlier investigators did not fully appreciate the possibilities of this location as an ideal place for normal tissue growth, but recently many authors have found the anterior chamber of the eye to be a suitable place to study the normal physiological responses of transplanted tissue.

In 1873, VanDooremaal transplanted the mucous membrane of the lip into the anterior chamber of the eye, and discovered a tendency toward cyst development in the transplant. Goldziehr followed with his report on the results of transplanted nasal membrane in 1874, and in 1890 Hansemann recorded the transplantation of embryonic tissue. From that time on until early in the twentieth century, it appears that little work of importance was accomplished.

Foremost in the recent literature are the names of Schochet, Neumann, Litt, Allen, Bauer, Priest, Podleschka, and Dworzak. These investigators, using principally the female sex organs, showed the comparative ease with which endometrial tissue will grow when transplanted to the anterior chamber of the eye. This situs is ideal because it offers excellent visibility for observation of the tissue, a good circulation for the transplant to grow, and provides easy recovery of the tissue for microscopic study.

For these reasons, it occurred to us that some constructive information could be obtained if pieces of the prostate gland were transplanted into the anterior chamber of the eye.

In this study, 20 male rabbits were used in varying ages from 8 to 12 months. Under ether anesthesia, the abdomen was opened by midline incision. The bladder was emptied by manual decompression and pulled up and out of the abdomen and retracted posteriorly. With an Ellis clamp, the seminal vesicles were grasped and pulled upward and then held in place by an assistant. The large bowel was freed as far down as possible from the base of the bladder and held down with a small sponge. The two arteries running upward along the outer border of the prostate and seminal vesicles were ligated low down near the neck of the bladder. This later technique, which was developed only recently in the course of the experiment, controlled to a great degree the bleeding and hemorrhage and made the process of enucleation of the prostate easier.

[1]Read at meeting of the North Central Urological Society, Cleveland, Ohio, November 8, 1934.

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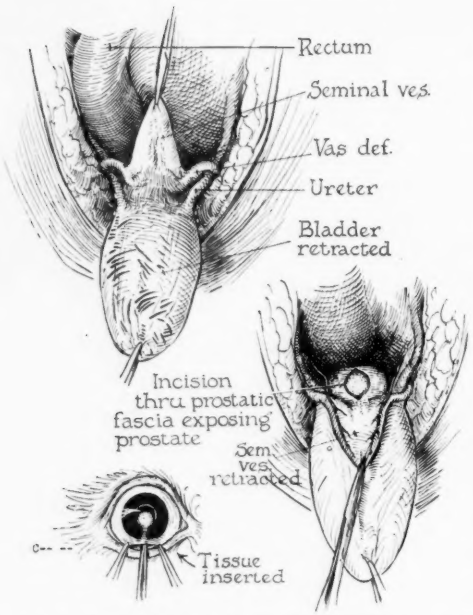

Fig. 1. Technique used in removing the prostate and inserting the piece into the eye. *c*, Incision at limbus with small piece of prostatic tissue being inserted underneath the cornea.

The prostate could now be distinctly seen beneath the fascia as a yellow mass. A midline incision was made through the fascia, and with a pair of forceps and a pair of small scissors the prostate was enucleated from its bed, and detached low down at the neck of the bladder. Great care was taken in order not to injure or squeeze the tissue. A small pack was then placed in the prostate bed for a few minutes to control the hemorrhage and then removed.

Several pieces of prostatic tissue, not more than ½ millimeter square, were then cut from the prostate and placed in a warm normal salt solution.

The eye was then prepared for the transplant by clipping the lid hair with an ordinary finger nail scissors. No antiseptic solution was used in the eye. With two small forceps with teeth, the eye was grasped near the limbus and slightly rotated upward. An incision 5 millimeters long was made through the cornea at the limbus with a cataract knife. Sufficient fluid usually escaped so that the intraocular tension was decreased enough to allow the implant to be easily inserted with the aid of a blunt spatula. No attempt was made to close the incision with catgut and the eye was left open. After a little practice the pieces could be inserted without a great deal of difficulty.

In presenting our results, a composite picture of the group is used rather than the gross and microscopic findings in each case.

A successful growth was obtained in 36 of the 40 eyes. Of the successful transplants, 10 became infected and were discarded. This is

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 2. *A*, Prostatic tissue 6 weeks after it had been transplanted.

Fig. 3. Transplant of prostatic tissue before injection of anterior pituitary-like hormone.

Fig. 4. Marked increase in the size of the transplanted prostate following administration of anterior pituitary-like hormone is shown. *A*, Prostate. *B*, Small cystic areas in prostatic tissue.

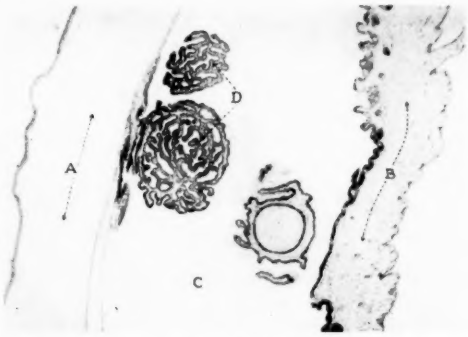

Fig. 5. Low power microscopic section of transplanted prostatic tissue. *A*, Cornea. *B*, Iris. *C*, Anterior chamber. *D*, Note the attachment of one piece of prostatic tissue to the cornea.

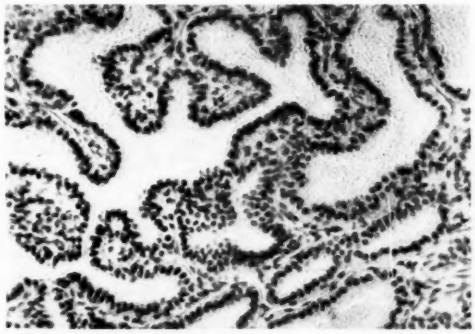

Fig. 6. High power view of *D* in Figure 5. Note normal structure of prostatic tissue.

the most important complication. The eyes of each rabbit were enucleated, under ether anesthesia, from 2 to 10 months after the prostate was transplanted; the rabbit was then immediately killed and autopsy performed.

The eyes were at once placed in Mueller's solution and left in this solution for 3 weeks, changing to fresh fluid several times. Then they were washed in running tap water for several hours, placed in a solution of 10 per cent formalin for 24 hours, and again washed in tap water. Each eye was run through 70 per cent, 80 per cent, 95 per cent, and 100 per cent alcohol for 24 hours; then removed from the alcohol and a window light opening about 1 centimeter square was cut in the back. Following this, it was put into a solution of absolute alcohol and ether for 24 hours, after which time the iris was removed. The eyes were then placed in thin celloidin for 5 weeks; into a thick solution of celloidin for several days, then blocked, labelled, and put in 80 per cent alcohol until ready for use.

When the tissue was cut, each section was placed on previously numbered small filter papers, thus keeping the serial numbers in proper order of cutting. These sections were kept covered at all times with 80 per cent alcohol. The usual standard staining methods were employed.

In our experiment, 850 sections were stained and studied.

From 12 to 14 hours after the prostatic tissue was placed in the anterior chamber, the eye showed a marked reaction as from a foreign body. There was profuse excretion and the conjunctiva was congested and red. A marked congestion of all the vessels at the limbus took place. Usually this acute reaction

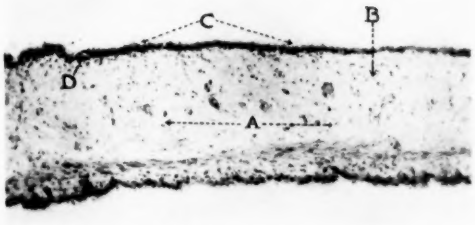

Fig. 7. Section of iris showing tendency of the prostatic tissue to proliferate along the surface. *A*, Iris. *B*, Anterior surface. *C*, Proliferation of glandular prostatic tissue along the surface of the iris. *D*, Tendency to form glandular structure. See Figure 8.

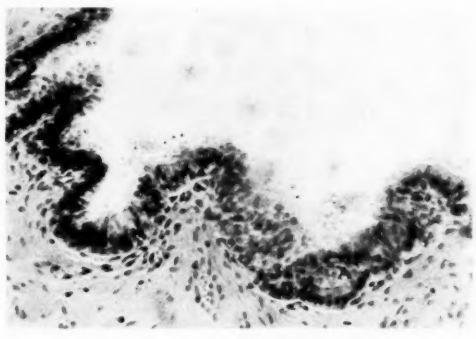

Fig. 8. High power view of region *D* in Figure 7. *A*, Tendency of cells to form glandular structures.

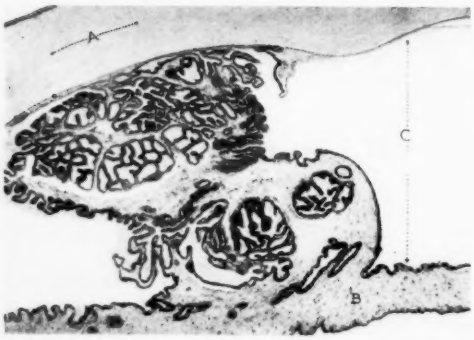

Fig. 9. Low power microscopic view of prostatic tissue after stimulation with anterior pituitary-like hormone. *A*, Cornea. *B*, Iris. *C*, Anterior chamber. *D*, Marked hyperplasia of the glandular structure.

Fig. 10. Microscopic view of another section of prostate gland transplant after stimulation with anterior pituitary-like hormone. *A* and *B*, Formation of large cystic spaces. *C*, Marked glandular hyperplasia.

subsided by the ninth day and definite dilated blood vessels could be seen centering about and entering into the transplanted tissue. During the next 3 to 4 weeks, in some of the eyes, there was an increased ocular pressure. From 6 to 8 weeks, changes were observed which we were able to interpret only after the eyes had been studied microscopically.

This finding was the appearance of small cystic spaces which grossly had a gray tinge varying from the size of a pin head to 5 millimeters in diameter. The microscopic structure of these epithelial lined cysts will be illustrated in the slides. These cysts did not cause any abnormal reactions.

Another interesting microscopic finding was the proliferation of a layer of columnar cells over the anterior surface of the iris on to the cornea. This epithelium was directly continuous with, and similar to, the glandular structure of the prostatic cells. (Fischer and Ebeling have shown experimentally in tissue culture that epithelium has the ability to form a delicate and continuous layer over the surface of artificial media.)

In those portions nearest the implant, it was high columnar and at the periphery the cells were often cuboidal. Many times this epithelium had the tendency to reproduce glandular structures resembling the original glandular structure of the transplant. This occurred always on the anterior surface of the iris and cornea and did not invade the stroma of these two structures.

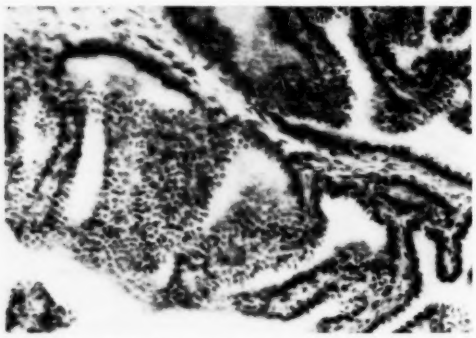

Fig. 11. High power view taken from *C* in Figure 10. Note marked proliferation of gland; many areas of cells four or five layers deep.

To extend our experiment further, a small group of rabbits were given daily injections of the anterior pituitary-like[1] hormone, and another group daily injections of antuitrin. These injections were started 10 to 12 days after the transplant and continued from 6 to 8 weeks. In those that had received the antuitrin, no noteworthy changes either macroscopically or microscopically could be seen. However, important gross and microscopic changes were observed in some of the eyes of the rabbits that received injections of the anterior pituitary-like hormone.

From the seventh to tenth day following the first injection, the transplant increased in size

[1]Antuitrin "S"—from Parke-Davis Co., Detroit.

and continued to do so until in several of the eyes, at the end of 3 to 4 months, they had covered one-half of the surface of the eye. Furthermore, it was observed that in the gross anatomical changes there was a marked increase in the vascular supply to the transplant, characterized by an increase in the number and size of the blood vessels. In the transplant itself there were many large translucent gray areas.

In the study of the micropathology, the following changes were observed: The formation of large cysts which corresponded grossly to the gray translucent areas. These cysts were similar to those which are frequently observed in the microscopic picture of benign prostatic hypertrophy. The cells lining these cysts were usually cuboidal; in some instances they were completely flattened in character. The second important change were areas where the glandular structure had undergone marked hyperplasia and hypertrophy. In many sections the glandular epithelium was three to four layers deep with an increase in the papillary arrangement of these cells.

SUMMARY AND CONCLUSIONS

1. The results of the autotransplantation of the prostatic tissue in the eyes of rabbits are recorded.

2. Pieces of prostatic tissue were transplanted and grew when they were placed in the anterior chamber of the eye of the rabbit.

3. The tissue maintained its normal structure.

4. The glandular cells proliferated along the anterior surface of the iris and reproduced gland-like spaces.

5. The ease of transplantation, constant visibility, a fluid filled space for growth and nourishment, and prompt vascularization lead us to believe that the anterior chamber of the eye is an ideal location for the study of transplanted prostate.

6. Preliminary observations from the use of the two pituitary-like hormones on the transplanted prostatic gland are given.

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ILEOCOLITIS

Acute Ileocolitis Simulating Appendicitis and Characterized by Edema of the Ileocecal Region and Mesenteric Glands; Its Relation to "Regional Ileitis" or "Chronic Cicatrizing Enteritis"

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IN the early weeks of 1934 there were admitted to the Hospital for Sick Children a number of cases in which the symptoms simulated those of acute appendicitis. These proved on subsequent investigation to be cases of acute ileitis or ileocolitis of a type such as we, or our immediate associates, had not previously encountered. This report deals with 3 such patients, who were operated upon following a pre-operative diagnosis of acute appendicitis and a fourth patient who was not subjected to surgical interference. This patient died and the postmortem findings are recorded. These 4 cases are chosen because clinically they were all under the care of one of us (A. W. F.) and because they represented the most exaggerated form of this condition. In addition to the 4 cases reported in detail, there have been several other milder cases admitted under the care of our associates. These cases are not reported fully, but are referred to later in discussing the serology.

Case 1. G. F., female, aged 8¾ years, was admitted January 27, 1934, and discharged February 6, 1934. Four days previous to admission, the patient complained of abdominal pain in the region of the umbilicus where it remained. She vomited practically everything during this period. There was no history of diarrhea. The patient had no recent nasopharyngitis. Admission temperature was 100.2 degrees F.; pulse, 128; respirations, 26. The patient did not appear acutely ill. The abdomen moved freely. There was tenderness in the right lower quadrant with considerable muscle spasm in this region. There was no rebound tenderness. No mass could be felt. The white blood count was 16,000; urinalysis, negative.

A diagnosis of acute appendicitis having been made, the patient was operated upon immediately. The cecum and terminal ileum were markedly swollen. The appearance was somewhat similar to that seen in an edematous bowel following the reduction of an intussusception of some hours' duration. The terminal 8 to 10 centimeters of the ileum measured about 4 centimeters in diameter and was very tense throughout. The lumen was practically obliterated. There was marked congestion of the serous surface except at the ileocecal junction where the bowel was so tense with edema that it was grayish-white in color. The Peyer's patches as felt through the bowel wall, were enlarged for several feet proximal to the ileocecal valve. They were oval in shape and measured about 3 by 2 centimeters and seemed about 3 millimeters thick. The superficial vessels in the mesentery were congested. The mesenteric glands were enlarged and firm, varying in diameter from 1 to 2 centimeters. Appendectomy was performed. Cultures taken from a small amount of free fluid in the abdomen were negative. Convalescence was uneventful, except for a temperature ranging to 100.4 degrees F., for 6 days. Examination of the appendix showed a rather abundant lymphoid tissue, with no evidence of acute or chronic inflammation.

Case 2. J. S., male, aged 10 years, was admitted January 30, 1934, discharged February 9, 1934. Two days previous to admission, the patient complained of abdominal pain which was cramp-like in character. This was generalized at first and then localized to the right lower quadrant. He was nauseated, but did not vomit. There was no history of diarrhea, previous attacks of abdominal upset, or of recent nasopharyngitis. Admission temperature was 99.2 degrees F.; pulse, 92; respirations, 24. The patient did not look acutely ill. The abdomen moved freely. There was considerable tenderness and muscle spasm in the right lower quadrant. There was no hyperesthesia and no rebound tenderness. No mass was palpated. The white blood count was 13,000; urinalysis, negative.

Acute appendicitis was diagnosed and the patient was operated upon immediately. The terminal ileum and cecum were almost solid with edema. The superficial vessels of the bowel and mesentery were injected. The distal 8 or 10 centimeters of the ileum formed a tubular mass with the lumen practically obliterated. The mesenteric glands were very large and firm. The Peyer's patches were also large. Cultures taken from a small amount of free fluid in the abdomen were negative. Appendectomy was performed. Convalescence was uneventful except that there was a continuous fever ranging from 99 to 100 degrees F., while he remained in the hospital. The microscopic findings in the appendix were similar to those in Case 1.

Case 3. R. B., male, aged 3 years, was admitted January 29, 1934, died February, 1, 1934. Eight

days previous to admission, the patient commenced vomiting. The parents stated that there was no complaint of pain at this time. He vomited occasionally for 3 days. A considerable amount of milk of magnesia was given, following which he had some fluid movements. The vomiting continued, he became distended, looked very ill, and was sent to hospital. There was no history of recent nasopharyngitis. Admission temperature was 100.3 degrees F.; pulse, 92; respirations, 24. The patient looked acutely ill. The tongue was dry. The abdomen was greatly distended. On palpation there was general abdominal tenderness which was greatest in the right lower quadrant. Here a firm mass could be felt about the size of an orange extending well out to the flank. The white blood count was 18,000; urinalysis, negative.

The patient was kept in bed in Fowler's position with heat to the abdomen and was given 5 per cent glucose in normal saline intravenously by the drip method. On the day following admission, the mass was larger. The temperature and the pulse had risen to 102 and 152 degrees, respectively. Operation was decided upon, but the child suddenly became very cyanosed. He was put in an oxygen tent. The following day a laparotomy was performed. The cecum was solid with edema and grayish-white in color. The terminal 10 or 12 centimeters of the ileum were also very edematous. Above this the Peyer's patches were very much enlarged. The mesenteric glands were swollen and firm, similar to those in Cases 1 and 2. Cultures which were taken from a small amount of clear free fluid in the abdomen were negative. The abdomen was closed without further operative interference. The child died on the following day. The temperature reached 105.4 degrees F., before death. No permission for a postmortem examination was obtained.

Case 4. A. W., female, aged 2½ years, was admitted January 30, 1934, died February 2, 1934. Four days previous to admission, the patient was "out of sorts" and commenced vomiting. Bowel movements had been regular. Purgatives were given 2 days before admission but there was no diarrhea even with these. There was a continuance of the vomiting and a complaint of abdominal pain. The patient became distended. There was no history of previous attacks of abdominal upset. The patient had had a slight head cold recently. Admission temperature was 104 degrees F.; pulse, 160; respirations, 32. The patient was drowsy and very toxic on admission. There was considerable distention of the abdomen. There was generalized abdominal tenderness, thought by some observers to be greatest in the right lower quadrant. No mass was felt. There was a vaginal discharge, which on culture yielded Bacillus coli in 24 hours. The white blood count was 13,000. The urinalysis was negative.

The patient was kept in bed with heat to the abdomen and given 5 per cent glucose in normal saline intravenously and sips only by the mouth. The temperature ranged from 104 to 106 degrees F. The respirations varied from 40 to 60, and the pulse up to 160. There were no bowel movements while in the hospital. The distention grew worse, the color became poor, and the patient died on the fourth day in the hospital.

Because of the apparent rarity of this condition, the postmortem findings will be described in some detail.

Autopsy findings. The examination was carried out 8 hours after death. Permission to examine the head was not obtained. The body was that of a well nourished, white female of about 2½ years of age, 35 inches (90 cms.) in height. The abdomen was protuberant and tympanitic. The only findings of interest in the chest were a few small patches of pulmonary collapse, very early bronchopneumonia, and a small atheromatous plaque in the aortic cusp of the mitral valve. The important findings were in the abdomen.

The peritoneal cavity contained about 250 cubic centimeters of almost clear, pale, amber-colored fluid in which were floating a very few small flakes of fibrin, particularly in the pelvis. The peritoneum for the most part was quite smooth and glistening but here and there in the region of the terminal ileum and cecum there were small patches with slight loss of luster. The coils of small intestine were greatly distended with gas. The striking feature was the presence of a marked edema of the wall of the intestine in the ileocecal region. This involved about 20 centimeters of the terminal ileum, the cecum, and about 8 centimeters of the ascending colon. The serous surface was pale and grayish-white except for an occasional vein coursing under the surface. The walls of this portion of the gut were extremely edematous, giving a doughy sensation on palpation. The appendix lay retrocecal in a horseshoe-shaped curve; its serosa was quite smooth, and it showed no gross evidence of disease. The mesenteric glands were very large, some of them measuring 1½ by 2½ centimeters. They were pale red and edematous. The lower border of the liver was high, lying 1½ centimeters above the right costal margin. The upper border was level with the third rib on the right side and the fourth rib on the left side.

The mucosa of the esophagus was somewhat reddened, and in places showed a slight granular appearance. The stomach appeared quite normal. It contained a small amount of light brownish, semi-fluid material. The mucous membrane appeared healthy. The duodenum and jejunum appeared normal, except for moderate congestion of the mucous membrane and rather marked distention with gas in the lower jejunum. The changes in the mucosa of the terminal 20 centimeters of the ileum were in marked contrast to the appearance of the serosa of this portion of the bowel, which was of a pale grayish white color, quite smooth, and still retained its luster, except for a few very small areas. Inspection of the inner surface of the bowel explained the cause of the doughy sensation elicited by palpation. The amount of edema was of an extreme degree, and was so

Fig. 1. Case 4. Terminal ileum, cecum, and proximal portion of colon. Note the swollen Peyer's patches, the ulceration of the ileum, the thickened ulcerated ileocecal valve, the marked edema of the mucosa of the cecum and the umbilicated swollen solitary lymph follicles in both ileum and colon. The insert shows a number of swollen mesenteric glands.

marked in the region of the ileocecal valve as to prevent the passage of gas or fluid through this aperture. The mucous membrane of the lower part of the ileum was only moderately injected. The Peyer's patches stood out very prominently (Fig. 1). In places they were from 2 to 4 millimeters in thickness; the epithelium over them was ulcerated and was covered with a thick, shaggy, grayish white pseudomembrane. Some of the patches were surrounded by a narrow zone of hyperemia. Scattered between them were numerous swollen lymph follicles in the mucous membrane. Many of these had a yellowish, necrotic, umbilicated center. Some of these also were surrounded by a zone of hyperemia. In the distal 6 centimeters of the ileum, the ulceration became confluent involving the whole of the mucosa, which was completely covered by a grayish yellow, shaggy pseudomembrane. The edematous thickening of the walls of the intestine was very marked in this region. Here the cut edge of the muscular portion of the wall had a pale, grayish white, semi-transparent appearance, while the cut edges of the Peyer's patches were mottled, dark red to grayish red. Removal of the pseudomembrane revealed a reddish granular surface: this membrane covered both proximal and distal surfaces of the ileocecal valve and extended into the cecum for a distance of about 1½ centimeters. Beyond this point, while the wall of the cecum and the proximal portion of ascending colon showed marked edema, the ulceration and pseudomembrane formation were confined to the solitary lymph follicles; many of these were greatly swollen, raised above the surface of the surrounding mucosa, had umbilicated centers, and were covered with grayish yellow membrane. Some of the smaller ones were surrounded by a zone of hyperemia. They were most numerous in the proximal 12 centimeters of the ascending colon with an occasional one near the hepatic flexure and one situated in the beginning of the transverse colon. The remainder of the large bowel appeared quite normal.

Fig. 2. Case 4. Cecum. Exudate on surface of mucosa. Hematoxylin and eosin stain, ×30.

The liver weighed 460 grams. On gross examination it appeared congested, and the cut surface was somewhat greasy. The spleen weighed 34 grams. Its surface was smooth and dark red. The cut surface appeared healthy. The kidneys weighed, right 64 grams, left 55 grams. The surface was smooth, of a brownish red color, and the stellate veins were rather prominent. The capsule stripped readily. The cortex and medulla appeared healthy. The ureters, bladder, suprarenals, and pancreas appeared healthy. Uterus, tubes, and ovaries were of the healthy infantile type.

The anatomic diagnosis was: acute pseudomembranous ulcerative ileocolitis; acute inflammation of ileocecal valve with stenosis; acute intestinal obstruction; acute mesenteric lymphadenitis; ascites; fatty liver; partial pulmonary collapse; early bronchopneumonia; atheroma of mitral valve; congestion of kidneys.

Microscopic examination. Section taken through the ileocecal valve and adjacent ileum and cecum showed the greater part of the mucosa to be ulcerated and covered with a thick layer of exudate composed of necrotic cells, fibrin, a few erythrocytes, and numerous colonies of bacteria (Fig. 2). In gram stained sections these bacteria proved to be gram negative bacilli. Here and there a few islands of epithelial cells still remained, but these stained poorly and showed varying degrees of necrosis. The lymphoid tissue had undergone marked necrosis. In places the greatly swollen Peyer's patches and soli-

Fig. 3. Case 4. Edge of Peyer's patch. Note the great depth of tissue between the muscularis mucosæ and the muscle coat; also the thick overhanging exudate on the surface of the mucosa. Hematoxylin and eosin stain, ×30.

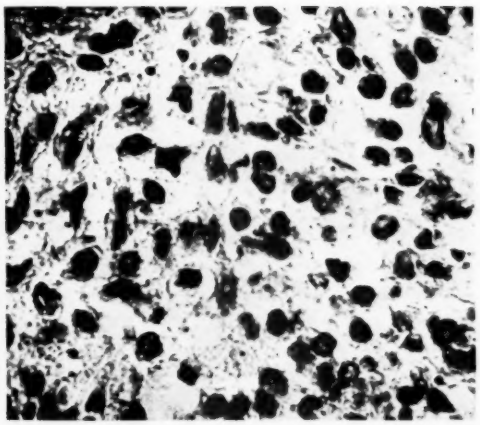

Fig. 4. Case 4. Photomicrograph of submucosa of terminal ileum, showing the type of cellular reaction. Note the scarcity of polynuclear cells. Hematoxylin and eosin stain, ×685.

tary lymph follicles remained as only necrotic shadows of their former structure, with here and there a few intact lymphocytes around their periphery (Fig. 3). One interesting feature was the comparative absence of polymorphonuclear leucocytes in the presence of such marked necrosis, such extensive fibrin formation, and such enormous numbers of bacteria. While a few leucocytes were seen, usually close to the mucosal surface, many of these had pyknotic nuclei. The infiltrating cells in the wall were sparsely scattered and were made up for the most part of large mononuclear cells with oval, pale staining vesicular nuclei (Fig. 4). These were interpreted as endothelial leucocytes. There were also scattered lymphocytes. Another striking feature was the degree of edema, particularly in the submucosa. This extended throughout the cecum and up the ascending colon, well beyond the areas of ulceration. It was this edema rather than the cellular infiltration which accounted for the marked increase in thickness of the wall of the colon (Fig. 5).

Many of the solitary lymph follicles also showed necrotic centers with ulceration of the overlying epithelium, giving the follicle a crater-like structure. This appearance was accentuated by the presence of a thick, fibrinous, necrotic membrane which was adherent to the rim of the crater and overhung its edges (Fig. 6). Sections stained for amebas according to the technique recently described by Meriwether were negative. The muscular portion of the wall appeared to suffer less severely than the other structures. In places it showed little change, while in those regions corresponding to the most extensive epithelial damage, there were varying degrees of intercellular edema, with infiltration with a few mononuclear cells. The muscle fibers themselves did not appear to be seriously damaged. In the subserosa also were varying degrees of edema and sparse cellular infiltration, while the serous surface for the most part appeared to escape. In only a few places could one see thin deposits of almost acellular fibrin on the serous surface. The blood vessels, on the whole, appeared to suffer but little. No change was noted in the arteries and arterioles. Some of the veins, however, particularly those adjacent to the more extensive necrotic areas were filled with thrombi, and in these regions too there were small areas of perivascular hemorrhage. The majority of the lymphatics

Fig. 5. Case 4. Section of colon. In lower part of field whole thickness of muscular portion of wall is shown. Between this and the muscularis mucosæ is the extremely edematous submucosa. Hematoxylin and eosin stain, ×30.

Fig. 6. Case 4. Section through solitary lymph follicle of colon. Note the depth of the necrosis, and the umbilicated nature of the lesion. Hematoxylin and eosin stain. ×30.

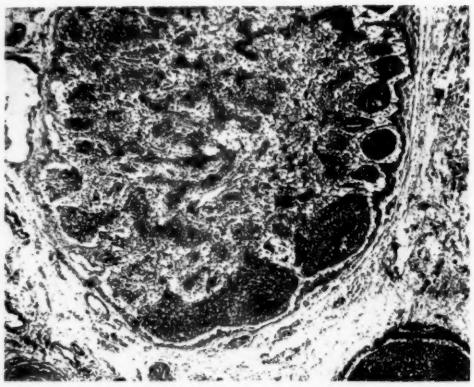

Fig. 7. Case 4. Mesenteric gland. Note the general alteration in structure and the extensive edema. Hematoxylin and eosin stain, ×25.

were dilated and contained a comparatively acellular, pink-staining, finely granular material.

The adjacent mesenteric lymph glands showed varying degrees of congestion and edema, particularly the latter (Fig. 7). To such an extent was this present that the general topography of the gland was greatly altered and the germinal centers in places were no longer recognizable as such. In addition, the lymph channels were widely dilated. Some appeared quite empty, while others contained varying numbers of large mononuclear cells. An occasional cell showing phagocytosis was seen, but this was the exception rather than the rule. Some of the smaller glands in the ileocecal angle showed in addition fairly marked necrosis. The general structure of the liver was but little altered. The cells of the liver cords, however, in the hematoxylin and eosin stained sections, showed quite marked granular degeneration with vacuolation. In sections stained with scarlet red, these vacuoles were found to be filled with fat. While this fatty change was noted in every cell, and in all portions of the lobule, it was most marked in the periportal regions. In the periportal connective tissues, and confined to these regions, there was considerable infiltration with lymphocytes and a few polymorphonuclears. Some of the bile capillaries appeared to be compressed. The lung showed small patches of collapse, some capillary congestion with acute bronchitis, and very early bronchopneumonia, associated with considerable subpleural edema. The spleen, kidney, myocardium, and pancreas showed no microscopic lesions worthy of note.

Bacteriology. Direct smears from the mesenteric lymph glands, liver, and gall bladder showed gram negative bacilli. These were present in quite large numbers in the gall bladder. As the body had been kept in the refrigerator from the time of death to that of autopsy, 8 hours later, these were thought not to be the result of postmortem invasion. From the above sources, as well as from the spleen, heart's blood, and ulcers in the ileum, there was recovered a bacillus having the following characteristics. It was gram negative, non-motile, fermented dextrose, mannite, maltose, lactose, and xylose with the formation of acid and gas. It fermented litmus milk, turned Endo's plates red, produced indol, reduced lead acetate, but did not liquefy gelatin. Except, therefore, for its non-motility it possesses the cultural characteristics usually ascribed to Bacillus coli which may at times also be non-motile. With the exception of the cultures from the ileum, which yielded also other intestinal bacteria, this was the only organism recovered.

In addition to the 4 cases described, there were admitted under the care of other members of the surgical staff several cases in which the symptoms were similar and the macroscopic findings at operation were only slightly less marked. A few cases also came under observation, which were thought to be similar in nature, but which were not submitted to operation. These cases are not reported in detail but from some of them serum was obtained for serological investigation as recorded below.

Unfortunately, at the time of the autopsy on Case 4 agglutination tests were not considered, and while blood was taken for culture, none was saved for subsequent agglutination tests. Such tests were carried out, however, with blood serum from Cases 1 and 2 and from several of the other patients who were suffering from, or had recovered from, what was thought clinically to be the same condition,

TABLE I.—AGGLUTINATION TEST WITH SERUM OF PATIENTS WITH ILEOCOLITIS AGAINST BACILLUS W. ON THE ONE HAND AND KNOWN MOTILE BACILLUS COLI ON THE OTHER HAND

	Bacillus W.						Known Bacillus coli					
	Serum dilutions 1 in						Serum dilutions 1 in					
	40	80	160	320	640	1280	40	80	160	320	640	1280
G. F. Case 1	−	−	−	−	−	−	+	±	−	−	−	−
Ja. Sm. Case 2	+	+	+	+	−	−	+	+	±	−	−	−
Ja. Su.	+	+	−	−	−	−	+	±	−	−	−	−
Ja. Do.	+	+	+	±	−	−	+	±	−	−	−	−
S. T.	−	±	±	±	+	+	+	±	−	−	−	−
Je. Me.	−	−	−	−	−	−	±	−	−	−	−	−

Control agglutination tests were also set up as follows (to simplify matters the organism recovered at autopsy will be referred to as Bacillus W.): (1) Serum from 6 patients (who were suffering from or had recovered from what was thought clinically to be the same condition) against Bacillus W. (2) Serum from these same 6 patients against a known strain of motile Bacillus coli. (3) Serum from 6 patients (who gave no history of recent ileocolitis) against Bacillus W. (4) Serum from 7 patients (also giving no history of recent ileocolitis) against a known strain of motile Bacillus coli.

The results of these tests are shown in Tables I, II, and III.

TABLE II.—CONTROL AGGLUTINATION TESTS WITH SERUM OF PATIENTS WITH NO ILEOCOLITIS AGAINST BACILLUS W.

	Bacillus W.					
	Serum dilutions 1 in					
	40	80	160	320	640	1280
A. B.	−	−	−	−	−	−
E. L.	−	−	−	−	−	−
D. L.	−	−	−	−	−	−
R. L.	−	−	−	−	−	−
W. P.	+	+	+	−	−	−
D. K.	+	+	±	−	−	−

TABLE III.—CONTROL AGGLUTINATION TESTS WITH SERUM OF PATIENTS WITH NO ILEOCOLITIS AGAINST KNOWN MOTILE BACILLUS COLI

	Known motile Bacillus coli					
	Serum dilutions 1 in					
	40	80	160	320	640	1280
B. S.	−	−	−	−	−	−
M. W.	−	−	−	−	−	−
G. M.	−	−	−	−	−	−
P. M.	−	−	−	−	−	−
M. C.	−	−	−	−	−	−
M. T.	−	−	−	−	−	−
M. M.	−	−	−	−	−	−

DISCUSSION

That one is here dealing with an acute infectious process, there can be little doubt. The nature of the infection, however, is by no means clear. In seeking to explain the picture, several questions naturally arise. Is this condition something new, or is it merely an exaggerated form of a disease previously recognized? Was the gram negative bacillus isolated from Case 4 the causative organism in that particular case? If so, what is the organism, and what is its relation to the other cases reported? Is there some other entirely different etiological agent, and is the bacillus recovered simply a strain of Bacillus coli which gained entrance to lymph glands, to portal circulation, and thence to liver and gall bladder simply by reason of the extensive destruction of intestinal mucosa? In the present state of our knowledge it is impossible to give a definite answer to any of these questions. That the bacillus is not merely a post-mortem invader, we believe can be concluded from its presence in large numbers in direct smears from gall bladder, the body having been kept in the refrigerator in the meantime. Whether it caused the disease is an entirely different matter. The evidence supplied by the serological tests is far from convincing. While the sera of 4 of the 6 other cases tested, agglutinated this bacillus in dilutions varying from 1:80 to 1:1280, in the remaining 2 no agglutination took place. Then too, 2 of the 6 controls agglutinated this organism in dilutions of 1:80 and 1:160, respectively. On the other hand, it should be pointed out that,

while all of the 6 cases showed slight agglutination with a known motile Bacillus coli, no agglutination was obtained with the sera of another control group of 7 patients against a known strain of Bacillus coli.

These results might be interpreted as meaning that Bacillus W. was the causative organism, that agglutinins against that organism were produced in 4 of the other 6 cases tested, that the organism is closely related to the colon bacillus, and for this reason there is some "group agglutination" with an ordinary strain of Bacillus coli. That this is the correct interpretation is by no means established. The series of cases as well as that of the controls is altogether too small to permit of any definite conclusions. Much more work remains to be done.

The lesion, it is true, bears a certain resemblance to that seen in some types of bacillary dysentery. In dysentery, however, the disease is usually more widespread. The cellular infiltration is greater, hemorrhages are more pronounced, the edema is less marked, and what is of much greater significance is the fact that the patients have frequent bowel movements. In the cases reported here diarrhea was conspicuous by its absence. This, in view of the degree of inflammation, is difficult to explain.

Clinically the disease has been repeatedly mistaken by us for acute appendicitis. To our knowledge there are no differentiating points in the history, physical examination, or laboratory findings. Postoperatively it has been noted that the increased temperature has returned to normal very slowly.

Thus far, we have failed to find in the literature any detailed reports of a similar condition. That the disease is closely related to that variously described as "regional ileitis," "chronic cicatrizing enteritis," or "benign granuloma of the intestines," we have great reason to believe. Increasing numbers of case reports under the headings mentioned are finding their way into the literature (1, 2, 4). The majority of the patients are adults and have come under observation when the disease has reached a chronic stage. In some the condition has simulated malignancy, and attempts have been made to indicate its benign nature by the use of such terms as "benign granuloma of the intestines" or "inflammatory tumor of the intestines." Undoubtedly, there have been included within this group conditions of varying etiology, but recently Crohn, Ginzburg, and Oppenheimer have attempted to separate what they believe to be a specific clinical entity, which they have designated as "regional ileitis." This condition is defined by them as "a disease of the terminal ileum affecting mainly young adults, characterized by a subacute or chronic necrotizing and cicatrizing inflammation. The ulceration is associated with a disproportionate connective tissue reaction of the remaining walls of the involved intestine, a process which frequently leads to stenosis of the lumen of the intestine, associated with the formation of multiple fistulas. The disease is clinically featured by symptoms that resemble those of ulcerative colitis, namely, fever, diarrhea and emaciation, leading eventually to an obstruction of the small intestine; the constant occurrence of a mass in the right iliac fossa usually requires surgical intervention (resection). The terminal ileum is alone involved. The process begins abruptly at and involves the ileocecal valve in its maximal intensity tapering off gradually as it ascends the ileum orally, for from 8 to 12 inches. The familiar fistulas lead usually to segments of the colon forming small tracts communicating with the lumen of the large intestine. Occasionally the abdominal wall anteriorly is the site of one or more of these fistulous tracts."

If the condition which we have described represents the early acute stage of what these observers designate as "regional ileitis," it at once becomes obvious that the definition given requires some modification. The majority of the cases reported by these authors were young adults, the oldest patient being 52 and the youngest 17. If, as is believed, the process is an inflammatory one, there would appear to be no reason why children should be immune. The ages in our series were as follows: 8¾ years, 10 years, 3 years, and 2½ years. The detailed pathological findings are from the youngest case.

Of greater difficulty of reconciliation is the location of the lesion. This according to

Crohn is the terminal ileum. He states "in this disease the rectum and colon are never involved." If this statement is correct, then the condition which we have described is obviously not one of regional ileitis. In none of our cases was the disease confined to the terminal ileum. In each instance there was some involvement of the cecum or colon. It should be pointed out, however, that in all 4 cases not only was the evidence of disease much greater in the ileum than in the colon, but that all of our cases were seen during the acute stage, while in all of the cases in which Crohn and his co-workers had an opportunity to study resected material "the patient had been ill for at least a year." Is it not possible that in some of these patients during the acute stage there may also have been some involvement of the cecum?

A glance at Figure 1 is sufficient to show that the ulcerative process is much more marked in the ileum, stopping almost abruptly at the ileocecal valve, although the edema of the colon is very pronounced. It is, therefore, quite conceivable that resolution in the colon might proceed to completion while the inflammatory process in the ileum might be progressive. In this connection also we should like to draw attention to the statement of Crohn that "the familiar fistulas lead usually to segments of the colon, forming small tracts communicating with the lumen of the large intestine." While such fistulous lesions involving the colon may usually commence as primary ulceration in adjacent coils of ileum, that they never develop from lesions primary in the colon may be very difficult to establish, so that the bald statement "that the terminal ileum is alone involved" is perhaps too sweeping.

Then too it should be pointed out that Harris, Bell, and Brunn, in discussing the nomenclature of this disease also question the advisability of limiting the disease process to the terminal ileum. In one of their reported cases, and in another not described in detail, the lesions "involved mainly the jejunum." They, therefore, suggest the more inclusive term of "chronic cicatrizing enteritis" and express the belief that with "more universal recognition by surgeons of this disease process other cases will be reported involving the jejunum as well as the terminal ileum." The same we believe may be said of the cecum and colon. However, while the name suggested by Crohn appears to be too limited, that suggested by Harris may on the other hand be too comprehensive. Recently under the title of "chronic cicatrizing enteritis" Donchess and Warren report a case with involvement of the entire cecum and ascending colon in a woman of 62 years, and present a synopsis of 24 other reported cases in which there is involvement of both cecum and colon. That these cases should all be included here is a question. While all may have shown a chronic cicatrizing process in some part or other of the intestinal tract, yet some of them (including their own reported case) appear to have been secondary to appendicitis. That such a condition should follow acute appendicitis with extension of the inflammatory process to adjacent cecum and colon is not inconceivable; but is this the condition that Crohn is attempting to isolate from what he calls the "hodge-podge or melting-pot in which are thrown all those benign inflammatory intestinal tumors, which are neither neoplastic nor due to a specific bacterial agent"? We think not. So that by whatever name this condition ultimately comes to be known, care must be taken that it be not too restrictive on the one hand or too comprehensive on the other hand.

Clinically, another apparent discrepancy requires consideration. According to Crohn one of the symptoms of "regional ileitis" is diarrhea; this was conspicuously absent in all our cases, except in Case 3, in which fluid movements were noted following the administration of milk of magnesia. Here again let us point out that most of Crohn's patients "had been ill from several months to 2 years before coming under observation," and very little is known or recorded of the symptoms in the earlier course of the disease. It is quite conceivable that as the disease progresses and ulceration and cicatrization become more marked a chronic diarrhea might develop, while inquiry into the history of these patients at the time of their acute illness might reveal the fact that diarrhea was not always a constant feature.

In the more acute cases to which Crohn refers, the findings as noted at operation are almost identical with what we have observed. In speaking briefly of the early phases of the disease, he states: "the latter (that is the early phases) are sometimes encountered at the operating table following an illness of from 1 to 2 weeks and diagnosed as a rule as acute appendicitis. At this time the terminal ileum is found thickened, soggy, and edematous; the serosa is a blotchy red. The mesentery of the terminal ileum is greatly thickened and contains numerous hyperplastic glands. Owing to the possibility of spontaneous resolution, resection has never been performed at this stage so that we have no knowledge of the intra-intestinal changes present at this time."

Unfortunately, he does not state whether any of these patients were followed and whether their subsequent history was in any way similar to that of the chronic cases which he describes. If, however, they do represent the acute stage of the disease, the striking similarity between his description and our own observations at least suggests that we are dealing with the same condition. If this assumption is correct, then the description of the "intra-intestinal changes" during the acute stage of the disease, which we have been fortunate enough to observe in Case 4, and which we have described in some detail, should add further to our knowledge of this subject. As for our non-fatal cases, these will be followed with interest and will be reported upon at a later date.

In the meantime it is thought advisable to place our findings on record in the hope that further interest in this disease, particularly in the acute stage, may be aroused, and its true etiology recognized. If this disease is of infectious origin, as we believe it is, the discovery of an etiological agent is much more likely to be made during the acute stage before there has been opportunity for widespread invasion by the normal flora of the intestinal tract. Conclusions based upon bacteriological investigation carried out during the chronic stage will probably be of little value.

SUMMARY

Four cases of acute ileocolitis with marked edema of the intestinal wall are reported, one with postmortem findings. The clinical resemblance of this disease to acute appendicitis is pointed out. Its relation to "regional ileitis," or "chronic cicatrizing enteritis" is discussed and it is suggested that the cases reported here may represent the acute phase of this condition. Its etiology remains obscure.

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THE EXPERIMENTAL PRODUCTION OF EXCESSIVE ENDOMETRIAL HYPERPLASIA[1]

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ABNORMAL uterine bleeding occurring just before or during the menopause and in the absence of gross pelvic lesions is frequently associated with a notable hyperplasia of the uterine mucosa. In some instances the glands are so greatly dilated that we are accustomed to speak of microscopic sections of such an endometrium as having a "Swiss cheese" pattern. By most authorities the hyperplasia in question is attributed to an ovarian disturbance characterized by an over secretion of estrin in the absence of corpora lutea. Indeed Witherspoon advances a step farther and postulates that the unopposed action of estrin on the uterus results both in immediate endometrial changes characterized by hyperplasia and in more latent myometrial pathology in the nature of fibromyomatous neoplasms.

There is definite experimental evidence which favors the first part of this view. Thus Hofbauer concluded from his experiments upon guinea pigs injected with alkaline extracts of pituitary glands that the internal secretion of the ovary is essential for hyperplastic changes ocurring in the upper part of the uterine mucosa, the "functionalis." On the other hand he holds that the basal layer, as judged by the response of this structure to repeated pituitary administration in ovariectomized animals, is under the control of the anterior pituitary. Fluhmann has demonstrated an excessive production of estrin during the course of endometrial hyperplasia and has suggested the name "hyperestrinism" to describe the condition. Again, Burch, Williams, and Cunningham operating upon two patients for hyperplasia of the endometrium failed to find corpora lutea in the ovaries of either. However, a follicular cyst was present in the ovaries of both patients. The fluid aspirated from these cysts was injected into spayed mice and rats. The changes previously found in the endometrium of each patient were similar in many respects to those found in the uterus of the experimental animals receiving the fluid from that patient.

In a second series of experiments Burch and his associates injected spayed rats and guinea pigs with varying amounts of estrin for an average period of 3 weeks, the daily average injection consisting of 25 rat units. A large percentage of the experimental animals showed characteristic cellular reactions of the endometrium as well as Swiss cheese dilatations of the glands. The microscopic appearances of the specimens were very similar to those of human hyperplasia of the endometrium. A further series of experiments was reported in which hyperplasia was brought about as the result of continued estrus produced by partial castration.

Definite experimental evidence that the unopposed and prolonged activity of estrin is capable of inducing a degree of endometrial hyperplasia sufficiently pronounced to warrant the designation "Swiss cheese hyperplasia" is up to the present available only for the guinea pig. The present paper is a report of the experimental production of this type of hyperplasia in two catarrhine primates, the chimpanzee (Pan satyrus) and the sooty mangabey (Cercocebus torquatus atys).

EXPERIMENTAL DATA

a. *Chimpanzee.* The experimental animal was an adolescent female that had been used in a study of the sexual skin (Zuckerman and Fulton, 1934). At the time of the experiment she was about 8 years old and though she had shown signs of ovarian activity (as judged by swelling of the sexual skin) for some 14 months, she had never menstruated. Bilateral gonadectomy was performed on September 29, 1933; the ovaries contained numerous small follicles, but no luteal tissue. Apparently the animal had never ovulated.

Between October 9 and October 28, 1933, estrin[1] was administered in gradually mounting doses until a total of 21,100 rat units had been injected. The maximum dosage given in a single day was 1000 rat units.

[1]The estrin preparations were very generously supplied by the Parke Davis Company through the courtesy of Dr. Oliver Kamm, and by the Schering Corporation through the kindness of Dr. Gregory Stragnell.

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Fig. 1. Photomicrograph showing endometrium of a chimpanzee at the end of a course of injections of estrin totaling 21,100 rat units. ×10

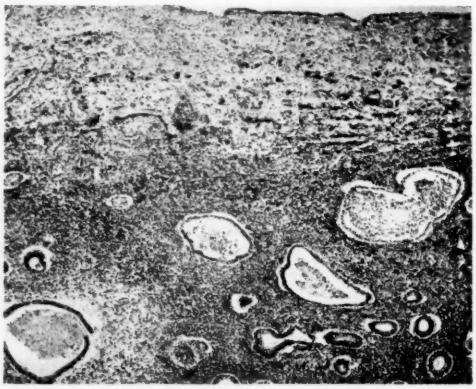

Fig. 2. Photomicrograph showing endometrium of a mangabey at end of a course of estrin injections totaling 33,675 rat units. Note the superficial zone of degeneration, and the dilated glands. ×40

The animal, which was in a poor and emaciated condition, was sacrificed on October 28. The reproductive organs were immediately fixed, and the following is a description of the uterus which after sectioning was stained with Meyer's hemalum and eosin.

Cystic dilatation of the glands, which are numerous, is displayed at all levels of the mucosa, and is visible to the naked eye, the condition extending from the two horns of the pseudobicornuate fundus as far down as the isthmus. Many of the glands are coiled and branched, and most are filled with secretion and cast off glandular cells. The surface epithelium is somewhat irregular, and not as tall as that of the glands, and its usually contracted nuclei are placed toward the free border of the cells. Some of the glandular epithelium is of a similar character, with the nuclei lying near the cell margin, and the deeper parts of the cells occupied by pale staining globules. On the whole, however, the glandular epithelium is a taller columnar type than the surface epithelium. In the deeper glands, the nuclei are more prominent than those nearer the cavum uteri, and they are usually situated somewhat away from the free margins of the cells. In the dilated and cystic glands the epithelium is irregular, in some places flattened, in others heaped. The appearances suggest that after degeneration or rupture of their lining cells, some of these glandular cysts discharged their contents into the cavum uteri by rupture of the surface epithelium, this process accounting for some of the irregularities in the latter and perhaps also for some localized accumulations of homogeneous eosinophilic material that are to be seen in the subepithelial zone. The stroma is tightly packed except toward the cavum uteri, where it is somewhat edematous. The mucosal blood vessels are dilated, but there are no extravasations of blood, nor can any of the stromal collections of homogeneous esoinophilic material be ascribed with any certainty to previous extravasations.

Cystic glands do not occur either in the isthmus, or in the cervical canal. In cross section the uterine lumen in the region of the isthmus has the shape of a six pointed star flattened from back to front; the epithelium of the surface of this part of the uterus equals in height and otherwise resembles that of the coiled glands, the nuclei lying toward the free margins of the cells, the cytoplasm of which is broken up into light staining globules. The epithelium of the cervical canal is similar in appearance, but taller. (Fig. 1.)

b. *Mangabey* (*Cercocebus torquatus atys*). The experimental animal was a fully mature sooty mangabey, one of the Old World monkeys, whose menstrual cycles had been followed for a year previous to a course of estrin injections. The average length of the ten preceding cycles was 31 days (range 29 to 36). Estrin injections were begun on the twelfth day of the eleventh cycle and given daily until a total of 33,675 rat units had been administered, the maximum amount administered on a single day being 2,000 rat units. Presumably as a result of these massive doses of the follicular hormone, the next menstrual period did not appear when expected and the cycle prolonged itself for 53 days. On the fifty-third day the animal died after an abrupt illness which lasted a week. Sections of the uterus were prepared and stained with Meyer's hemalum and eosin. The histological appearances were as follows:

The uterus. The greatest depth of endometrium in any part of the stained preparations is 2.5 millimeters. The muscular layers of the uterus appear healthy but the mucosa presents a picture of unusual degeneration.

The superficial third of the endometrium is considerably degenerated and appears as a somewhat homogeneous vacuolated eosinophilic matrix em-

bedded in which are stromal and epithelial cells in all stages of degeneration. Completely degenerated glands are also represented in this zone. The blood vessels of the area are intact, however, in spite of the degeneration of the tissues surrounding them. At no point in the uterus, which was sectioned at various levels, was any extravasation of red blood cells seen.

The surface epithelium is mostly intact, but the majority of the cells, which are arranged in a single layer, have undergone pronounced vacuolar degeneration. Very little is left of the cells in those places where this process has proceeded farthest, although the basement membrane remains intact even in such regions. The degenerated remnants of surface epithelium, and presumably of cells of the superficial third of the mucosa as well, can be seen in the lumen of the body of the uterus.

The degenerated superficial zone grades into more healthy basal endometrium, which has a tightly packed stroma.

The uterine glands are numerous, and are mostly straight. Many are dilated and slightly coiled, and some are even cystic. In the basal zone of the endometrium, the narrow, elongated, highly chromophilic nuclei of the glandular epithelium occupy the greater part of the cell bodies. The nuclei in more superficial zones are generally situated in the middle third of their cells, separated from the basal third by clear vacuoles, and from the free margins of the cell by granular eosinophilic cytoplasm. The basal vacuolation appears to represent degeneration and not secretion; it seems to be the first step toward the total disintegration of the cell bodies, the next being the vacuolation of the granular cytoplasm which lies superficial to the nuclei.

Cystic glandular changes are confined to the body of the uterus and do not extend beyond the isthmus. There is practically no degeneration in the cervical canal, the epithelium and glands appearing relatively healthy. In this region of the uterus, both the surface and the glandular epithelium is high columnar, and both the main uterine lumen and the glands, some of which are greatly dilated, are filled with mucus, in which are numerous leucocytes which can also be seen penetrating the cervical epithelium.

The ovaries. The ovaries of this animal were sectioned serially. They presented the typical appearance of ovaries removed from animals which have been treated with estrin. They were small, follicular growth had been retarded, and there was a great deal of follicular atresia. No functional corpora lutea were present, and the only remains of such tissue were old and degenerated corpora obviously belonging to cycles preceding the one in which the animal was injected with estrin. (Fig. 2.)

To our knowledge endometrial degeneration of the extent and character presented in this specimen has not before been described as accompanying the administration of estrin. The appearance of the tissues makes it unlikely that the pathological appearance of the endometrium was due either to postmortem changes or to changes brought about in the preparation of the sections. It is possible that the change was due to the very large dose of estrin administered, and it is also conceivable that the degeneration was an accompaniment of the acute and brief illness that preceded the animal's death. Whichever may have been the case, the factors which brought about this picture of degeneration are immaterial from the point of view of this discussion. From our present point of view, the important fact is the existence in this mangabey of considerable endometrial hyperplasia as indicated by the numerous glands of the mucosa and more particularly by cystic dilatation. The extent of the latter change is not as great as that which is shown by the chimpanzee described. Nevertheless, the amount of hyperplasia and glandular proliferation is far greater than has previously been described as following the injection of estrin into monkeys.

EVALUATION OF PREVIOUS EXPERIMENTAL WORK

With respect to previous experimental work upon Primates: Edgar Allen injected a spayed Macacus rhesus over a period of 22 days with a total dosage of 1065 rat units of lipoid and aqueous extracts of human placenta and of liquor folliculi from pig ovaries. At the end of the experiment the endometrial glands were extremely long and showed considerable coiling and branching in the tips next to the internal muscular layer. In a further series of experiments a total of 550 rat units of extracts from human placenta and from liquor folliculi of pig ovaries was administered to three ovariectomized monkeys over a period of 24 days. The animals were then killed on the first, third, and fifth days after the last injection. The uterine mucosa of the animals killed on the first and third days after the last injection was pearly white, spongy, and edematous. That of the monkey killed on the fifth day was in an early menstrual stage. Histological sections showed a typical early menstrual endometrium.

Robertson, Maddux, and Allen injected ovarian hormones into 4 ovariectomized adult

female monkeys. In 1 a total of 447 rat units of lipoid extract of human placenta in oil solution was administered over a period of 48 days. In the 3 other animals, the period of injection lasted from 24 to 27 days, and the total dosage ranged from 882 to 981 rat units. In 2 animals corpora lutea were also implanted. Two experimental menstrual periods followed the cessation of injections of the estrus producing ovarian hormone. Sections of the uteri showed typical menstrual endometria of the non-ovulating type. Three implants of recent human corpora lutea did not increase the growth of the endometrial glands beyond the interval stage. In all these studies endometrial hyperplasia did not proceed beyond the point characterized by long tubular glands.

As far as we are aware only Werner and Collier have studied the effect of estrin upon the human endometrium. These authors administered to 5 women previously subjected to bilateral ovariectomy, a total dosage of 25,200 rat units of theelin over a period of 84 days. A histological examination of the curettings obtained following this treatment showed an increase in the amount of endometrial tissue and the presence of hyperplastic glands which were irregular in form and similar to the glands found in endometrial hyperplasia of the human uterus. The hyperplasia produced, however, was far less than that manifested by the chimpanzee and mangabey which form the subject of this report, and about the same as that induced in the studies on monkeys which are cited in the preceding paragraph.

As was noted in the introduction to this paper, the lesion under discussion is generally believed to result from a disordered ovarian activity. Indeed, in many patients who complain of menorrhagia and in whom a hyperplastic condition of the endometrium is found, corpora lutea are absent from the ovaries and in addition it is found that the ovaries present cystic changes. It is assumed, therefore, that the hyperplastic lesion of the endometrium is due to the unopposed action of estrin.

In this connection the investigations of Smith and Smith are of interest. These authors found that progestin prepared according to the method of Corner and Allen causes the excretion of injected estrin in rabbits. In a further study upon 8 women, 4 of whom presented an amenorrhea, 3 of whom were sterile, and 1 of whom was normal, Smith and Smith concluded that as in rabbits, estrin is excreted only when the human organism has been exposed to the action of corpus luteum. In 2 of their patients, 1 a woman who had been completely amenorrheic for 3 years, there was a ± reaction on the twenty-fourth and twenty-eighth days of the cycle for the excretion in the urine of estrin given orally. In the second patient, who had had no menstrual flow since a pregnancy 2 years previously, there was a consistently negative reaction for the excretion of estrin given orally. The results in both these cases were interpreted by Smith and Smith as indicating that no corpus luteum was present during the period over which these patients were tested. The results which were obtained by these authors also suggest that estrin is most effective in the absence of corpora lutea.

As noted herein, corpora lutea are absent from the ovaries of many women in whom menorrhagia is associated with a glandular hyperplasia of the endometrium. This clinical finding, taken together with the investigations of Werner and Collier and those of Smith and Smith, and with the results which were obtained following the administration of 21,100 rat units of estrin to a castrated chimpanzee and of 33,675 rat units of estrin to a normal monkey support the hypothesis that the unopposed action of estrin plays an important rôle in the production of glandular hyperplasia of the endometrium.

SUMMARY

The present paper is a report of the experimental production of an excessive endometrial hyperplasia, identical in all macroscopic and microscopic characters with the Swiss cheese hyperplasia of human pathology, which occurred in a castrated adolescent chimpanzee following a course of estrin injections totaling 21,100 rat units and in a normal mangabey monkey after a course totaling 33,675 rat units.

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EXPERIMENTAL STUDIES ON THE EFFECTS OF THE PERFORATION OF PEPTIC ULCERS[1]

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THE following description of the condition that develops after perforation of a peptic ulcer is given by Homans in his *Textbook of Surgery:*

> The symptoms of an acute perforation into the free peritoneal cavity begin with a sudden, agonizing epigastric pain, always associated with evidences of shock, and usually accompanied by vomiting. . . . The pain, at first, is localized but soon becomes general. Pallor is marked, the face drawn, the skin cold, the respiration shallow, the abdomen retracted and of a boardlike rigidity. The peritoneal insult is more sudden and violent than that caused by any but the most unusual instances of appendicitis, and tenderness, sharply localized over the region of the ulcer, usually can be brought out. At first the temperature is subnormal, the pulse little elevated. In the face of such a clean-cut emergency, it would hardly matter that no earlier story of ulcer could be obtained. However, the disease is not always so plainly labelled. Perforation in the course of an alcoholic spree is confusing; perforation upon an empty stomach, though unusual, causes symptoms of comparative mildness, and some duodenal perforations closely simulate appendicitis. In these latter, the duodenal content leaks out principally into the right abdomen, causing local tenderness and spasm. Thus there may occur epigastric pain, followed by pain, soreness, and muscular resistance in the lower right abdomen—a picture of appendicitis.

The experiments to be described in this paper were performed in an effort to find the factors which are responsible in the main for early severe signs and symptoms that follow the perforation of ulcers. Further, studies were performed in an attempt to determine the mechanism by which the circulatory collapse takes place in order that the alterations might be compared with those that are obtained in experiments in which shock is produced by other means.

For purposes of this study, it seemed inadvisable to produce a perforation of the stomach or duodenum, as this would have introduced the operation and the anesthetic as complicating factors. Also, this method does not allow one to determine which of the fluids that escape into the peritoneal cavity are responsible for the ill effects. Therefore, a condition similar to that which is observed following the perforation of a peptic ulcer was produced by injecting singly or in various combinations the different upper intestinal juices as collected from other dogs.

METHODS

Bile was obtained by cannulating the common duct after having ligated and divided the cystic duct. It was collected in a balloon which was attached to the dog by the method of Rous and McMaster. Pancreatic juice was collected in a similar way from a cannula that was placed in the main pancreatic duct after having ligated and divided the accessory duct by the method of Elman. The duodenal secretion was obtained by placing a cannula in a closed loop of the duodenum which had been freed of its bile and pancreatic connections. The continuity of the intestinal tract was restored by anastomosing the stomach to the jejunum. The secretion from the stomach was collected by making a closed pouch of the lower two-thirds of the stomach into which a cannula was placed. The upper portion of the stomach was then anastomosed to the jejunum.

The balloons in which the various secretions were collected were emptied daily into sterile containers. The fluids were tested as to sterility on blood agar plates.

The fluids were injected in varying amounts and in varying combinations into the peritoneal cavities of unanesthetized animals. Syringes of 20 cubic centimeter capacity and medium sized needles were used for the introduction. Alterations in the general behavior of the animals, in the pulse rate, and in the hematocrit readings were observed. In the experiments in which death occurred, the appearance of the intraperitoneal structures was noted and the quality of the free fluid in the peritoneal cavity was determined.

In the experiments in which the effects on the circulation of the intraperitoneal injection

[1]From the Department of Surgery of Vanderbilt University. Aided by a grant from the Fluid Research Fund of The Rockefeller Foundation

of the various fluids were studied, determinations of the cardiac output, pulse rate, maximum and minimum arterial blood pressures, blood concentration, femoral and splenic arterial inflow rates, and the body temperature were performed. Morphine was used as the anesthetic in these experiments. After having performed the control determinations, varying quantities of bile or pancreatic juice or both were injected into the peritoneal cavity, and another set of studies was made shortly thereafter. Additional determinations were carried out at approximately hourly intervals throughout the course of the experiments.

The cardiac output determinations were carried out according to the Fick principle. The arterial blood was collected under oil from the femoral or carotid artery and mixed venous blood was obtained from the right heart. The determinations of the oxygen content of the blood were carried out with the Van Slyke-Neill apparatus. The oxygen consumption was measured with the Benedict spirometer. A cannula, which was placed in a femoral artery and connected to a mercury manometer, was used in determining the blood pressure. Maximum and minimum valves were used. Hematocrit readings were determined by the use of Van Allen tubes. The arterial inflow rates were performed by the method which was described by Bartlett and modified by Erlanger.

At the completion of the experiments, the animals were killed painlessly and autopsied. The intraperitoneal structures were examined and the quantity of free fluid in the peritoneal cavity was determined.

RESULTS

I. The effects of the intraperitoneal injection of the fluids on the general condition of the animals, the survival period, and the blood concentration.

All of the animals became ill following the introduction of rather large quantities of one or more of the upper intestinal juices. Vomiting usually occurred shortly following the injection. The animals appeared weak and there was usually an early and significant increase in the pulse rate. The condition then seemed to improve for a while as has been described by Homans in instances of perforation in the human.

A. The effects of pancreatic juice. Death did not occur in any of the 9 experiments in which uninfected pancreatic juice was introduced into the peritoneal cavity. The quantity that was injected varied from 11 to 39 cubic centimeters per kilogram of body weight. In most of the experiments, there was a moderate increase in the concentration of the red blood cells. No difference in the effects of pancreatic juice obtained shortly after the operation and that a week later was observed. Death occurred in 3 of the 4 experiments in which infected pancreatic juice was used. The quantity that was introduced varied from 10 to 20 cubic centimeters. The length of time separating the injection and death was less than 24 hours in 2 of these experiments and 3 days in the 1 remaining. A great deal of free fluid was found at autopsy in the peritoneal cavity.

B. The effects of bile. The studies in which bile was used were more difficult to evaluate because the effects seemed to vary somewhat according to length of time elapsing between the operation in which the common duct was cannulated and the time at which the sample of bile for injection was collected. For example, the use of 11 cubic centimeters of bile per kilogram of body weight from a dog which had been operated upon 1 day previously resulted in death, whereas the giving of 20 cubic centimeters of bile per kilogram of body weight 6 days later from the same animal did not cause death. In other words, the bile becomes less toxic per unit of volume as the length of time separating the operation and the collection increases. For the first several days following the cannulation of the common duct, the bile is thick in consistency and it later becomes quite thin.

Nineteen experiments were performed in which the effects of the introduction of bile were studied. All of the animals appeared quite sick immediately following the injection and it was my impression that they were somewhat sicker than the animals in which corresponding amounts of pancreatic juice were introduced. In only 6 of these experiments had the operation on the animal from which

the bile was obtained been performed 4 days or less previously. The quantity of bile that was given per kilogram of body weight in the different experiments was 6.4, 11.0, 15.0, 15.0, 20.0, and 21.3 cubic centimeters. The only animal which died was the one in which 11 cubic centimeters per kilogram of body weight had been given and death occurred in 24 hours. The hematocrit reading increased from 41.0 to 61.7 per cent. Autopsy revealed the presence of 265 cubic centimeters of blood tinged fluid in the peritoneal cavity and a great deal of reddening of the structures there. A moderate increase in the hematocrit reading took place in the 5 remaining experiments in none of which death occurred.

That infection may be an important factor is illustrated by the results of an experiment in which organisms were introduced intentionally into bile that was obtained from an animal which had been operated upon 12 days previously. Death took place 40 hours following the introduction of this bile in the amount of 10 cubic centimeters per kilogram of body weight. As a control, it was found that the injection of 37 cubic centimeters per kilogram of body weight of uninfected bile from the same animal did not produce death. However, the recipient of the bile appeared quite ill for the first 24 hours.

C. The effects of the injection of equal amounts of bile and pancreatic juice. Twenty-two experiments were performed in which the effects of the injection of equal amounts of bile and pancreatic juice were studied. All of the animals appeared to be quite ill following the injection and there was an increase in the pulse rate and usually vomiting. There was very little change in the hematocrit reading in some experiments while a rather marked increase was observed in others.

Eleven of the 22 experiments will not be considered further because of infection of the bile or pancreatic juice or the elapse of too long an interval between the cannulation of the duct and the obtaining of the specimen for the injection. In the 11 remaining experiments, 7 of the animals survived the injection and 4 died as a result of it. The total quantities of bile plus pancreatic juice, in terms of body weight, that were injected in the 4 experiments in which death occurred were 17.5, 15.0, 20.0, and 20.0 cubic centimeters. The corresponding figures for the 7 experiments in which recovery took place were 10.0, 10.0, 10.0, 16.0, 10.0, 15.0, 20.0 cubic centimeters.

Autopsies on the animals which died showed striking changes. There was a great deal of reddening of all of the peritoneal surfaces and usually an extreme degree of fat necrosis. The fat necrosis in some instances extended above the diaphragm. Free bloody fluid was present in the peritoneal cavity in varying amounts. The small vessels in the peritoneal cavity were definitely dilated.

Although it is a point that is difficult of absolute proof, it seemed quite definite that a combination of bile and pancreatic juice exerted more untoward effects than an equal volume of bile or pancreatic juice alone. The action of the combination was undoubtedly greater than that of an equal quantity of pancreatic juice alone.

D. The effects of gastric juice. Nine experiments were performed in which the effects of the injection of gastric juice were studied. The introduction was usually followed by an acceleration of the pulse rate and a change in the appearance of the dog. A slight increase in the concentration of the blood occurred. None of the animals died as a result of the injection of gastric juice. The quantities introduced per kilogram of body weight varied from 7 to 26 cubic centimeters. In 5 of the experiments, the amount was greater than 20 cubic centimeters per kilogram of body weight.

It seemed very definite from these experiments that the injection of gastric juice is less harmful than the introduction of an equal volume of bile alone or a mixture of bile and pancreatic juice.

E. The effects of secretion from the duodenum. Three experiments were performed in which secretion from the duodenum was introduced into the peritoneal cavities of other dogs. There was slight infection present in each instance. None of the recipients died. The quantities introduced per kilogram of body weight were 8.0, 14.0, and 16.0 cubic centimeters.

II. The effects of the injection of the fluids on the cardiac output, blood pressure, and ar-

terial inflow. Eighteen experiments were performed in which the cardiac output and the maximum and minimum arterial blood pressures were determined before and at varying intervals following the introduction of bile or pancreatic juice or both. A comparison of the studies made at intervals varying from 6 to 30 minutes following the intraperitoneal injection with those performed during the control period shows that both the cardiac output and the maximum blood pressure had declined in 10 of the experiments while a decline in the blood pressure without significant alteration in the cardiac output had taken place in the 8 remaining experiments. It is my belief that the blood pressure declined prior to the drop in cardiac output in all or most of the experiments, but the latter determinations cannot be performed rapidly or repeatedly enough to determine this point. The decline in the minimum pressure which was present in 12 experiments was less than that in the maximum and hence there was a decrease in the pulse pressure. In the 6 remaining experiments, the minimum pressure did not drop.

Further studies were carried out at intervals varying from 40 minutes to 2 hours following the intraperitoneal injection. As compared with the control determinations, there was a decline in the cardiac output and maximum arterial blood pressure in all experiments. The minimum arterial blood pressure was the same as it had been during the control period in 6 experiments, it was slightly higher in 3, and definitely depressed in 9 experiments. A comparison of these determinations performed after an average time of 91 minutes following the intraperitoneal injection with those made shortly after the injection shows that the output of the heart had decreased in 17 of the 18 experiments. The maximum arterial blood pressure had increased in 4 of the experiments, it remained the same in 6 and decreased in 8. The minimum arterial blood pressure increased in 8 of the studies, remained the same in 3, and decreased in 7. The pulse pressure during this period was less than that observed previously.

Although there is some variation in the results of the experiments, in general it can be stated that the most significant early alteration in the circulation following the intraperitoneal injection of bile or pancreatic juice is a decrease in the arterial blood pressure and particularly in the maximum pressure. The output of the heart has usually declined rather greatly an hour or more later without much further alteration in the blood pressure.

An average of the determinations in the 18 experiments gives the following results. During the control period, the cardiac output was 1,356 cubic centimeters per minute, the maximum arterial blood pressure was 163 millimeters mercury, and the minimum blood pressure was 87 millimeters mercury. After an average interval of 14 minutes following the intraperitoneal injection, the average output of the heart was 1,090 cubic centimeters per minute, the maximum blood pressure was 110 millimeters mercury, and the minimum pressure was 75 millimeters mercury. After an average interval of 91 minutes following the injection, the average cardiac output was 688 cubic centimeters per minute, the maximum blood pressure was 100 millimeters mercury, and the minimum pressure was 76 millimeters mercury. The results of a representative experiment are given in Table I.

In some instances the bile or pancreatic juice was infected. The quantity of these fluids that was introduced into the peritoneal cavity in the different experiments varied from 172 to 380 cubic centimeters. The quantity of fluid recovered from the peritoneal cavity at the completion of the experiments varied from 200 to 605 cubic centimeters. The total quantity of bile or pancreatic juice or both that was introduced in all of the experiments was 4,823 cubic centimeters and the total quantity of fluid that was present in the peritoneal cavity at the completion of the studies was 7,715 cubic centimeters. The average quantity injected in cubic centimeters per kilogram of body weight was 20.8 and the average quantity of fluid present later in the peritoneal cavity was 33.3 cubic centimeters per kilogram of body weight. In addition there were small amounts of free fluid in the pleural cavities in some experiments. The duration of these studies varied from 2 to 7 hours, the average duration being 4½ hours. Nine of the animals died and the

remainder were killed painlessly at the end of the observation period.

A fairly wide variation in the arterial inflow rate was observed during the control period and it is my opinion that alterations which were observed subsequently are probably without significance. The femoral arterial inflow rate was determined in 20 experiments. The inflow rate remained approximately the same following the introduction of bile or pancreatic juice or both into the peritoneal cavity in 12 experiments; it increased somewhat in 7; and decreased in 1. The inflow rate as studied in the splenic artery was determined in 9 experiments. There was no definite change in 6 of these and an increase in the 3 remaining. It is to be remembered that an increase in inflow rate indicates a decrease in arterial tone and a decrease in arterial inflow indicates an increase in arterial tone.

EVALUATION

When a duodenal ulcer perforates into the free peritoneal cavity, there escapes through the opening a mixture of bile, pancreatic juice, gastric juice, duodenal secretion, saliva, and food and liquids, if such are present in the stomach. The quantity of these substances which escapes depends upon the amount of the material present in the stomach at the time, the size of the opening in the duodenum, and the length of time during which it maintains a free communication with the general peritoneal cavity. The amount of infection that is present in the material that escapes into the peritoneal cavity undoubtedly influences to an important extent the chances of recovery of the patient. This was demonstrated conclusively in some of the present experiments in which organisms were introduced intentionally. However, the early signs and symptoms appear too rapidly for infection to be a major factor and it is this stage of the process in which we are particularly interested in this paper. It was apparent at the beginning of the studies that many complicating factors would be introduced by making an opening into the duodenum and allowing the secretions to flow into the peritoneal cavity. These would include the anesthetic and the operation, and furthermore one would not be able to differentiate between the effects of the various types of secretions. It was for these reasons that it was deemed advisable to obtain the secretions from one group of animals and to inject them into a second group.

The experiments which have been described showed very clearly that the introduction of either bile or pancreatic juice or gastric juice or duodenal secretion in large amounts causes signs and symptoms in animals similar to those observed in the human following the perforation of a peptic ulcer. An immediate change in the condition of the animals was observed following the injection; they then seemed to improve for a while and later became quite ill again. Bile seemed to exert more deleterious effects than an equal volume of any one of the other secretions but the most marked changes followed the introduction of a mixture of bile and pancreatic juice. The reason for this is not apparent but it seems possible that the pancreatic juice is activated by the bile, thus increasing the total of the effects.

Horrall (8) has noted that the toxicity of bile varies directly with its salt content and specific gravity, and hence that gall bladder bile has a greater toxicity than hepatic duct bile or fistula bile. He (7) found that the injection of bile obtained from the gall bladders of dogs into the peritoneal cavities of other dogs in amounts of 5 cubic centimeters or more per kilogram of body weight caused death within 24 hours. Sterilized bile exerted the same effects.

The initial signs and symptoms that were observed following the intraperitoneal injections appear too early to be explained by the absorption of toxic material. It seems likely that the most important of the early actions of the juices is that of a chemical irritant. This results in a dilatation of the many small intraperitoneal vessels and I believe that it is brought about mainly by direct action on the vessels rather than through nerves, although both methods are probably concerned.

In previous studies (9), it has been shown that secondary shock which is produced by trauma to muscles or the slow withdrawal of blood is associated with first a decline in the output of the heart which is followed later by a decline in the blood pressure. The altera-

TABLE I.—EFFECTS OF PANCREATIC JUICE ON THE CIRCULATION

Time	Hematocrit	Pulse rate per min.	Temperature F.	Arterial O_2 vols. %	Venous O_2 vols. %	A. V. dif. vols. %	Max. B.P. mm. hg.	Min. B.P. mm. hg.	O_2 consumption c.cm. per min.	Cardiac output per min. c.cm.	Arterial inflow c.cm. per min.
10:55 a.m. control	36.6	80	98.3	15.84	11.46	4.38	150	92	73.80	1685	10.3
11:45 13 min. after injection	41.7	155		16.19	11.52	4.67	101	70	63.84	1367	10.3
1:30 2 hours after injection	47.7	190	99.7	17.62	10.62	7.00	110	89	61.25	875	6.9
2:50	50.4	200		20.20	6.54	13.66	48	42	43.54	319	10.1

Protocol. Experiment 18. 8:15 a.m., morphine gr. 1. 10:55, control determinations. 11:29 to 11:32, 285 c.cm. of infected pancreatic juice introduced into the peritoneal cavity. 11:45, second group of determinations. 2:50, further determinations. 3:45, animal died. Autopsy revealed general reddening of all of intraperitoneal structures. There were 430 c.cm. of blood tinged fluid in the peritoneal cavity and 15 c.cm. of fluid in each side of the chest.

tions appear in the reverse order when primary shock (2) is produced. In approximately one half of the present experiments, the first determinations following the intraperitoneal injections showed a decrease in both the cardiac output and the blood pressure. In the remaining studies, the early change consisted of a decline in the blood pressure without appreciable alteration in the cardiac output. If methods were available for determining the output of the heart rapidly and repeatedly, I believe that this latter finding would have been observed in most or all of the experiments. At any rate, the alterations in the circulation that occur immediately following the injection of the various secretions appear to be similar to those that are found in primary shock. The studies which were carried out an hour or longer following the injection showed very little change in the blood pressure from that observed immediately after the injection whereas there was a decided decrease in the output of the heart. This phase of the disturbance in the circulatory system is similar to that observed in secondary shock.

My conception of the alterations in the circulation which follow the introduction of these secretions into the peritoneal cavity is as follows: A dilatation of many small vessels is produced by direct contact with the irritating solutions and, to a lesser extent, through nervous agencies. This results in a drop in the blood pressure. After the blood volume decreases as a result of the marked increase in the circulatory bed and the passage of fluid into the peritoneal cavity, the output of the heart diminishes. The blood pressure is probably prevented temporarily from declining further by vasoconstriction elsewhere.

The escape of fluid from the vessels into the peritoneal cavity is great enough to cause a considerable decrease in the blood volume but not sufficient to account for the entire decline. As to whether or not this quantity added to that which accumulates in the many dilated vessels is sufficient, one cannot state, as there is no accurate method for measuring it.

I have previously attempted a classification (3) of acute circulatory failure from a physiological viewpoint. The various types were classed as hematogenic, neurogenic, vasogenic, and cardiogenic. The condition under consideration does not fall into any single one of these types but is rather a combination of the first three. It is my impression that the early phase is largely vasogenic and the later stage is mainly hematogenic.

SUMMARY

Experiments were performed in an effort to find the factors which are responsible in the main for the rapidly developing signs and symptoms that follow the perforation of peptic ulcers. The alterations in the circulation which are produced by the introduction into the peritoneal cavity of the various upper intestinal juices were studied.

Bile, pancreatic juice, gastric juice, and duodenal secretion were obtained by cannulating the various structures. The juices were

injected with a syringe and needle into the peritoneal cavities of other dogs.

The following results were obtained:

1. Following the injection of rather large amounts of one or more of the upper intestinal juices, the animals became ill almost immediately. There was usually an increase in the pulse rate and vomiting.

2. Death did not occur in any of the 9 experiments in which sterile pancreatic juice varying in amounts from 11 to 39 cubic centimeters per kilogram of body weight was injected. Infected pancreatic juice in smaller quantities produced death.

3. Bile that is recovered the first several days following the cannulation of the common duct exerts more ill effects when injected into the peritoneal cavity than that which is collected later. Six experiments were performed in which uninfected bile obtained from animals operated upon less than 4 days previously was injected into other animals in amounts equalling 21 cubic centimeters or less per kilogram of body weight. All of the recipients became quite ill but only 1 died. Bile apparently exerts more untoward effects than an equal quantity of pancreatic juice.

4. Eleven experiments were performed in which equal quantities of uninfected bile and pancreatic juice were injected into the peritoneal cavity. The amounts introduced were closely comparable to those injected in the studies in which bile or pancreatic juice alone was used. Four of the animals died and it seemed quite definite that the combination of bile and pancreatic juice is more toxic than an equal volume of either of them.

5. Death did not occur in any of the 9 experiments in which a corresponding quantity of gastric juice was used or in the 3 experiments in which duodenal secretion was injected. These 2 secretions seemed to result in less harm than a corresponding quantity of bile alone or a combination of bile and pancreatic juice.

6. All of the animals which died as a result of the introduction of one or more of the secretions, exhibited marked reddening of the intraperitoneal structures. This reddening and the presence of massive fat necrosis was particularly marked in the experiments in which the mixture of bile and pancreatic juice was injected. There was usually a large quantity of free fluid in the peritoneal cavity at autopsy but this quantity by itself alone was not sufficient to account for the decline in blood volume and death. It is possible that this quantity plus the blood that was present in the many dilated intraperitoneal blood vessels might be sufficient. The increase in the concentration of the red blood cells in some experiments was very great while in others it was not marked.

7. Studies on the cardiac output and blood pressure were performed before and following the injection of bile or pancreatic juice or both. Although the results were not identical in all cases, the major early alteration consisted of a decline in the blood pressure, as is found in primary shock, and the subsequent change consisted of a greater drop in the cardiac output than in the blood pressure, as is found in secondary shock.

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FURTHER QUANTITATIVE DETERMINATIONS OF PROLAN AND ESTRIN IN PREGNANCY

With Especial Reference to Late Toxemia and Eclampsia[1]

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In a previous communication (1) we reported the results of quantitative analyses for prolan and estrin in the serum and urine of 42 women during the last third of pregnancy. Ninety-six per cent of the toxemic and eclamptic patients showed excessive amounts of prolan and 69 per cent of them had low levels of estrin—as compared with the figures derived for normal late pregnancy.

The purpose of the present paper is to record additional data on 27 more pregnant women. Six of the patients who showed no toxic symptoms had monthly specimens analyzed throughout pregnancy and the report of monthly analyses on a patient who developed toxemia at the eighth month is reprinted from the previous paper (Table I). The data on 9 additional cases of late pregnancy toxemia, 6 of whom had convulsions, are also given. We have been especially interested in discovering whether or not quantitative analyses for prolan and estrin might be of diagnostic value: (1) in differentiating between preeclamptic and nephritic toxemia; (2) in predicting the development of toxemia in later pregnancy; (3) as a means of prognosis in patients with clinical signs indicating the beginning of late pregnancy toxemia. Thus far 12 women (besides Cases 1 to 7, Table I), upon whom we have made serum analyses in the middle third of gestation, have been followed clinically to delivery (Table II) with these ideas in view.

The methods of collecting and analyzing specimens have been the same as those described previously (4). The urinary prolan and estrin are expressed in rat units per 24 hour volume and the serum prolan in rat units per 100 cubic centimeters, the figures being based upon the smallest amount of the urine or serum that gave a definitely positive test according to our standards. The limited quantity of blood available made it necessary to test for estrin each amount of a given serum upon only one or two spayed female rats. The data on serum estrin, therefore, are given in terms of the actual readings, +++ signifying a full estrous smear in one or both rats, ++ a pre-estrous reading, etc.

QUANTITATIVE ANALYSES THROUGHOUT PREGNANCY—TABLE I

In all 7 of the cases given in Table I, a peak in the level of prolan in serum and urine is noted during the second, third, or fourth month followed by a marked drop. In 5 of the 6 cases who developed no toxic symptoms, the prolan remained low throughout the rest of gestation. The level of estrin in these 5 cases rose as pregnancy advanced, reaching a peak during the last month. Case 7, on the other hand, showed a marked rise in serum prolan during the sixth month accompanied by a drop in urinary estrin. It was nearly 2 months later that the slightest possible trace of albumin appeared in her urine, but by 2 weeks before term, toxemia had become definite (hypertension, edema, and albuminuria) and forced delivery was considered advisable. Because of the findings in this case as compared with normals, we became apprehensive when Case 6 began to show a slight rise in serum prolan and a drop in estrin at 7½ months. At 8½ months the urinary prolan also had increased and the estrin of serum and urine were even lower. This patient, however, had not the slightest evidence of toxemia, had an induced delivery somewhat before due, and a normal puerperium. The apparent contradiction in these 2 cases can perhaps be explained by the fact that Case 6 delivered 1 month after the prolan estrin imbalance appeared, whereas Case 7 showed her imbalance earlier and developed no toxemia until nearly 2 months afterward. Case 6 was the only normally pregnant woman, both in this group and

[1]The Mrs. William Lowell Putnam investigation of the toxemias of pregnancy.

TABLE I.—QUANTITATIVE ANALYSES THROUGHOUT PREGNANCY ON 7 WOMEN, 6 WITHOUT AND 1 WITH LATE PREGNANCY TOXEMIA

Case 1. Normal. Mrs. A.R.W.

Case History	Date of specimen and clinical condition at time	Prolan		Estrin							
		Serum	Urine	Serum							Urine
		r.u. per 100 c.cm.	r.u. in 24°	1 c.cm.	2 c.cm.	3 c.cm.	4 c.cm.	5 c.cm.	6 c.cm.	10 c.cm.	r.u. in 24°
Age 30; II-para; first pregnancy normal; last catamenia 12-4-32; due 9-10-33; delivered normally on 8-28-33	1-23-33—1½ months—normal		700								175
	3-7-33—3 months—normal		1300								570
	4-6-33—4 months—normal		700								830
	5-8-33—5 months—normal		900								1500
	6-9-33—6 months—normal		800								3500
	7-14-33—7 months normal		500								4000
	8-13-33—8 months normal		800								5200

Case 2. Normal. Mrs. W.C.B.

Age 41; VII-para; first pregnancy, normal; three miscarriages at third month; threatened miscarriage for 1st 4 months of two pregnancies; last catamenia 11-29-32; due 9-4-33; induced labor 9-15-33	1-20-33—1¾ months—occasional uterine cramps. Nausea	200	13000							—	108
	3-2-33—3 months—occasional uterine cramps. Nausea	100	7900							—	120
	4-15-33—4½ months—normal	50	290							—	480
	6-20-33—6½ months—normal	33.5	450			—	+±	+++			750
	8-16-33—8½ months—normal	40	650	+±	++±	+++					7200

Case 3. Threatened Miscarriage. No toxic symptoms. Mrs. P.G.B.

Age 32; IV-para; 7 yrs. ago—normal pregnancy; 5 yrs. ago—irregular catamenia, menorrhagia, pelvic pain, resection of both ovaries for cysts; 4½ yrs. ago—miscarriage at 3 mos.; 1½ yrs. ago—miscarriage at 3 mos.; last catamenia 1-16-33; due 10-23-33; induced labor 10-28-33	3-17-33—2 months—nausea and vomiting	333	1700							—	<50
	3-22-33—2¼ months—nausea and vomiting	333	1700							—	<50
	4-14-33—3 months—nausea	200	1700							—	98
	6-12-33—5 months—intermittent staining and uterine cramps. No nausea	100	1180				—	++			2000
	9-9-33—7¾ months—normal. No symptoms since 6-16-33	40	600			±	+++				4000
	10-1-33—8½ months—normal	50	700	±	++±	+++					6000

Case 4. Threatened Miscarriage. Premature delivery at 7½ months. No toxic symptoms. Mrs. S.

Age 32; III-para; first pregnancy normal; second, miscarried at 3 months; last catamenia 5-21-33; due 2-25-34; spontaneous delivery 1-13-34	6-23-33—1 month—normal	<40	100							—	0
	7-18-33—2 months—nausea. Intermittent staining	333	2300							—	13
	8-10-33—2¼ months—nausea. Intermittent staining	200	2000							—	67
	9-6-33—3½ months—some nausea	66.6	700							—	118

TABLE I.—QUANTITATIVE ANALYSES THROUGHOUT PREGNANCY ON 7 WOMEN, 6 WITHOUT AND 1 WITH LATE PREGNANCY TOXEMIA—Continued

Case 4. Threatened Miscarriage. Premature delivery at 7½ months. No toxic symptoms. Mrs. S.—continued

Case History	Date of specimen and clinical condition at time	Prolan		Estrin							
		Serum	Urine	Serum							Urine
		r.u. per 100 c.cm.	r.u. in 24°	1 c.cm.	2 c.cm.	3 c.cm.	4 c.cm.	5 c.cm.	6 c.cm.	10 c.cm.	r.u. in 24°
Age 32; III para; first pregnancy normal; second, miscarried at 3 months; last catamenia 5-21-33; due 2-25-34; spontaneous delivery 1-13-34	10-10-33—4½ months—normal	40	280					—		+++	1560
	11-9-33—5½ months—normal	33.3	330			—		+++			1275
	12-9-33—6½ months—normal	50	700								2400
	1-9-34—7½ months—	50	530			—		+++			2700
	1-10-34—ruptured membranes. No mechanical explanation Delivery 1-13-34										
Case 5. Normal. (Mild hypertension when not pregnant.) Mrs. C.P.											
Age 34; II-para; first pregnancy 13 yrs. ago; sterility for 9 yrs.; B.P.140 when not pregnant; last catamenia 9-4-33; due 6-11-34; normal delivery 6-7-34	12-15-33—3½ months—B.P.150. Otherwise normal. Weight 125 lbs.	66.6	920							—	230
	1-12-34—4½ months—B.P.140. Otherwise normal. Weight 126 lbs.	1000	5900							—	850
	2-16-34—5½ months—B.P.140. Otherwise normal. Weight 130 lbs.	333	2000			—		++±			1000
	3-9-34—6 months—B.P.140. Otherwise normal. Weight 130 lbs.	100	1150								1900
	4-6-34—7 months—B.P.140. Otherwise normal. Weight 137.5 lbs.	40	960			—		+++			4000
	5-15-34—8 months—B.P.142. Otherwise normal. Weight 145.5 lbs.	50	350		+	+++					4000
Case 6. Normal. Mrs. A.L.P.											
Age 29; III-para; first two pregnancies 5 and 7 years ago, normal; last catamenia 8-10-33; due 5-17-34; delivered 5-5-34	11-5-33—2¾ months—some nausea	200	2040							—	<60
	12-4-33—3¾ months—normal	100	500					—		—	570
	1-2-34—4½ months—normal	66.6	364					—		—	850
	2-5-34—5½ months—normal	66.6	400			—		+++			870
	3-5-34—6½ months—normal	66.6	700	—	++±						5000
	4-2-34—7½ months—normal	100	700		—	++±					2350
	4-30-34—8½ months—normal	143	2000			—		++±			1300
***Case 7. Toxemia developed during last month. Mrs. M.**											
Age 33; II-para; toxemia at 8th month of last pregnancy; last catamenia 10-26-32; due 8-2-33; forced delivery due to toxemia 7-22-33	1-12-33—2½ months—vomiting B.P.130 Alb. o	333	1400					—	±		700
	2-13-33—3½ months—vomiting B.P.118 Alb. o	333	2100					+±	+++		760
	3-16-33—4½ months—well B.P.120 Alb. o	125	900			++	+++	+++			2700

*Reprinted from *Am. J. Physiol.*, 1934, 107: 137.

TABLE I.—QUANTITATIVE ANALYSES THROUGHOUT PREGNANCY ON 7 WOMEN, 6 WITHOUT AND 1 WITH LATE PREGNANCY TOXEMIA—Continued

*Case 7. Toxemia developed during last month. Mrs. M.—continued

Case History	Date of specimen and clinical condition at time	Prolan		Estrin							
		Serum	Urine	Serum							Urine
		r.u. per 100 c.cm.	r.u. in 24°	1 c.cm.	2 c.cm.	3 c.cm.	4 c.cm.	5 c.cm.	6 c.cm.	10 c.cm.	r.u. in 24°
Age 33; II-para; toxemia at 8th month of last pregnancy; last catamenia 10-26-32; due 8-2-33; forced delivery due to toxemia 7-22-33	4-11-33—5½ months—well B.P.112 Alb. o	100	640		+	+++					2100
	5-9-33—6½ months—well B.P.128 Alb. o	500	640		±	++±					1070
	6-5-33—7½ months—well B.P.118 Alb. o	200	730	—	++	+++					2400
	6-27-33—8 months—well B.P.126 Alb.SPT	500	3800	+±	++±						5900
	7-3-33—Alb. ST and edema of ankles										
	7-10-33—8½ months—edema of ankles B.P.140 and St alb. for last 2 weeks		5000								3300

*Reprinted from *Am. J. Physiol.*, 1934, 107: 137. S. T., slight trace; S. P. T., slightest possible trace.

in the 15 normal cases already reported (4), whose serum prolan after the sixth month was over 100 r. u. per 100 cubic centimeters, and it was not until the eighth month that hers exceeded this figure. At present we feel that the vital period, in which important information can be derived from quantitative estimations of prolan and estrin, is between the sixth and seventh months and that any marked variation at this time may indicate the development of future complications.

From the data presented in Table I, it is apparent that during the early months of pregnancy there are wide individual variations in the quantities of these two hormones. It is thus difficult to relate any particular clinical picture of early gestation to these substances. For example, Cases 2, 3, and 4 had miscarried previous pregnancies and threatened to miscarry the pregnancies herein reported. Case 4 had a premature delivery at 7½ months and Case 23 (Table II) had one at 6 months. From the hormone values on these 4 patients, we are unable to associate any endocrine picture with miscarriage. However, 5 of the group comprising Table I, Cases 2, 3, 4, 6, and 7, complained of nausea or vomiting during the early months. The low levels of estrin in 4 of them and the marked rise which accompanied the cessation of these symptoms in all 5 seems more than coincidental. This common complaint usually disappears by the fourth or fifth month at the time when estrin has reached a comparatively high level. The possibility of using this hormone therapeutically recommends itself.

QUANTITATIVE ANALYSES ON 9 CASES OF LATE PREGNANCY TOXEMIA, 6 OF WHOM HAD CONVULSIONS

CASE 8. Mrs. A.Z., aged 23, I-para. Last catamenia in January, 1933. Patient was admitted to the hospital August 12, 1933, in coma, about 7 months pregnant. She had had 40 to 50 convulsions in the previous 24 hours. Her blood pressure was 170/110. The urine contained a heavy trace of albumin with casts. There was edema of face and ankles. Blood specimen was taken on admission. Urine was obtained by catheter for 14 hours, then complete suppression. She died August 14, 1933. Clinical diagnosis, confirmed by autopsy, was eclampsia.

Serum prolan: 10,000 r.u. per 100 c.cm.

Urinary prolan: 970 r.u. in 24-hour volume (calculated from creatinine and patient's weight).

Serum estrin: test negative with 3, 4 and 5 c.cm.

Urinary estrin: 1300 r.u. per 24-hour volume (calculated from creatinine and from the patient's weight).

This case was included by Cushing (1, Case 5) in his report of hypophyseal changes associated with eclampsia and other hypertensive states. Her pituitary showed the basophilic invasion of the posterior lobe which he considers characteristic. Her serum prolan was the highest we have yet found; i.e., 0.01 cubic centimeter gave a markedly positive Aschheim-Zondek test. In all of the normal pregnancies that we have studied, at 7 months at least 1.0 cubic centimeter of serum was required to give a positive test. Moreover, the estrin content of her serum was low. It is probable that the urinary values are considerably lower than they would have been had the analyses been performed on an earlier specimen, since at the time of collection the kidneys had almost completely shut down. This case well confirms our hypothesis that a marked excess of prolan and a subnormal level of estrin are typical of eclampsia.

CASE 9. Mrs. H.K., aged 40 years, V-para. Previous pregnancies had been normal. Last catamenia was June, 1933. She was admitted to the hospital January 30, 1934, in coma and 7½ months pregnant. A history of convulsions at home was obtained. Three convulsions occurred after admission. Blood pressure was 190/110. The urine contained a heavy trace of albumin. The patient had been well until January 28, when she felt dizzy and noticed that her legs were swollen. Delivery occurred on January 31. The urine was collected for 24 hours after delivery and blood was taken at end of this period. Her blood pressure dropped to normal, eye symptoms disappeared and by February 11 the urine contained only the slightest possible trace of albumin. Clinical diagnosis: eclampsia.

Serum prolan: 1000 r.u. per 100 c.cm.
Urinary prolan: 4350 r.u. in 24 hours.
Serum estrin: negative with 5 c.cm.
Urinary estrin: 100 r.u. in 24 hours.

Here again the excess of prolan, in spite of the fact that these specimens were collected after delivery, is marked. It is known that the estrin level drops very quickly after delivery (5) and therefore the figures for estrin are probably considerably lower than they would have been a day earlier.

CASE 10. Mrs. M.S., aged 36 years, I-para. Last catamenia was June 25, 1933. Due April 1, 1934. On February 27 the blood pressure was normal; the urine contained a trace of albumin. After 8 days on hospital routine the patient was discharged, there being a slightest possible trace of urinary albumin. She re-entered on March 28 vomiting and with epigastric pain and headache. Blood pressure was 198/110. Urine contained heavy trace of albumin. She had two convulsions, one before labor was induced on March 28 and one after. Blood was taken at delivery. Clinical diagnosis: eclampsia.

Serum prolan: 1000 r.u. per 100 c.cm.
Serum estrin: positive with 3 c.cm.; negative with 2 c.cm.

Excessive serum prolan characterized this case; the serum estrin was on the low side of normal.

CASE 11. Mrs. A.K., aged 33 years, VIII-para. All previous pregnancies had been normal. Last catamenia was June 7, 1933. Due March 14, 1934. She was admitted to the hospital March 4; 8½ months pregnant. She had had headaches and scotomas for 3 weeks and epigastric pain for 2 days. One convulsion occurred after entry. Blood pressure was 210/120. The urine contained a heavy trace of albumin with casts. There was generalized edema. Blood was taken immediately after convulsion. Delivery occurred March 5, 1934. Toxemia disappeared. Clinical diagnosis: eclampsia.

Serum prolan: 200 r.u. per 100 c.cm.
Serum estrin: positive with 3 c.cm.; negative with 2 c.cm.

As has been pointed out (4) the degree of excess of prolan in toxemia does not always run parallel with the severity of symptoms. This patient's prolan, although considerably higher than the normal, was not as high as that of many of the pre-eclamptic cases. It may be that certain women are more sensitive to an endocrine imbalance than others. Another and more likely possibility is that by the time symptoms appear, placental changes may have taken place, with consequent decreased production of prolan and that, if analyses had been made earlier, the excess of prolan would have been more pronounced.

CASE 12. Mrs. M.McD., aged 33 years, VII-para. Previous pregnancies had been normal. The last catamenia was July 4, 1933. She was admitted to the hospital February 27, 1934; 7½ months pregnant. Blood pressure was 140/100. The urine showed trace of albumin with casts. Blood non-protein nitrogen was 72 milligrams per 100 cubic centimeters. The patient had headaches, dizziness, severe pain in right upper quadrant of the abdomen, and an inflamed parotid gland. Premature delivery occurred on February 27. Twelve hours postpartum there were convulsions. Complete anuria ensued. Blood was taken at the time of convulsions.

March 5, 1934: blood non-protein nitrogen, 120; creatinine, 6.5; uric acid, 8.9.

TABLE II.—ANALYSES ON 12 WOMEN IN THE MIDDLE THIRD OF PREGNANCY WHOSE CLINICAL PROGRESS HAS BEEN FOLLOWED TO DELIVERY

Case History	Date of specimen and clinical condition at time	Follow-up	Prolan		Estrin						
			Serum	Urine	Serum						Urine
			r.u. per 100 c.cm.	r.u. in 24°	1 c.cm.	2 c.cm.	3 c.cm.	4 c.cm.	5 c.cm.	6 c.cm.	r.u. in 24°
Case 17 E.R. Age 21; I-para; last catamenia 1-1-34; due 10-8-34	7-16-34—6 months—normal	No toxic symptoms Normal delivery at term	66.6	940		±	++±				1560
Case 18 E.P. Age 19; I-para; last catamenia 10-6-32; due 7-13-33	4-28-33—6½ months—normal	No toxic symptoms Normal delivery at term	66.6	900		—	++±		+++		2700
Case 19* Mrs. McA. Age 28; I-para; last catamenia 11-3-32; due 8-10-33; diabetes insipidus	5-12-33—6 months—normal	Received pituitrin daily throughout pregnancy	66.6	405			+±	+++			1800
	6-14-33—7 months—normal	No toxic symptoms Normal delivery at term		580							2700
Case 20 Mrs. E.M. Age 25; V-para; 1 living child; 2 miscarriages at 3 mos.; 1 miscarriage at 6 mos.; last catamenia 5-20-33; due 2-27-34	11-5-33—5½ months—normal	No toxic symptoms Spontaneous delivery 1-18-34 of a 5-weeks' premature viable infant	100	270			—		+++		1300
Case 21 Mrs. J.D. Age 41; XI-para; eclampsia with last pregnancy; all others normal	3-30-34—5½ months—Severe frontal headaches, scotomata, epigastric distress, drowsiness; no edema B.P. 210/130 Alb. VLT Blood N.P.N. 54.0	Nephritis Forced delivery 4-3-34 B.P. 4-30-34—190/100	66.6			—	—		+++		
Case 22 Mrs. A.A. Age 24; I-para; last catamenia 7-24-33; due 5-1-34	2-21-34—7 months—B.P. 152/98 Albumin—none Edema of ankles	Edema and high B.P. cleared up in 1 week under treatment Remainder of pregnancy normal Normal delivery 4-15-34	50.0		—	++±	+++				
Case 23 Mrs. P.C. Age 23; I-para; last catamenia 8-22-33; due 5-29-34	2-14-34—6 months—Flowing. No previous signs of threatened miscarriage. No albumin, hypertension, nausea or toxic symptoms	Premature labor 2-16-34 Non-viable fetus of 1 lb. 6 oz. Convalescence normal	200	1500		—	+++				1000
Case 24 Mrs. M.W. Age 26; I-para; last catamenia 7-12-33; due 4-18-34	1-13-34—6 months—edema B.P. 146/76 Alb. 0	Subsequent B.P. and urine analyses normal. No further toxic symptoms	200			—	+++				
	2-27-34—7½ months—normal	Premature delivery 3-11-34	100		—	+++					
Case 25 Mrs. I.K. Age 27; I-para	1-27-34—5 months—B.P. 140/85 Albumin, 0 Headaches for 2 weeks	Hypertension persisted throughout pregnancy B.P. normal after delivery	1000			—	++±				
	2-27-34—6 months—B.P. 140/90 Alb. 0	3-27-34—ST alb. No albumin after that date. No symptoms Normal delivery 6-4-34	333		—	++±					
Case 26 Mrs. M.F. Age 22; II-para; first pregnancy normal except for slight hypertension; last catamenia 6-16-33; due 3-20-34	1-29-34—7 months—B.P. 160/110 Alb. SPT No edema, headaches, dyspnea, or vomiting Hypertension and albuminuria began early in pregnancy	B.P. 140/150 and SPT alb. during rest of pregnancy Normal delivery 3-19-34 Clinical diagnosis: mild chronic nephritis	100					—	++±	++±	

*The results of analyses on the 5-12-33 specimens of this patient have been previously reported (4).

TABLE II.—ANALYSES ON 12 WOMEN IN THE MIDDLE THIRD OF PREGNANCY WHOSE CLINICAL PROGRESS HAS BEEN FOLLOWED TO DELIVERY—Continued

Case History	Date of specimen and clinical condition at time	Follow-up	Prolan		Estrin						
			Serum	Urine	Serum						Urine
			r.u. per 100 c.cm.	r.u. in 24°	1 c.cm.	2 c.cm.	3 c.cm.	4 c.cm.	5 c.cm.	6 c.cm.	r.u. in 24°
Case 27 Mrs. D.M. Age 33; IV-para; first pregnancy normal; has had toxic symptoms with 2 pregnancies; last catamenia 6–16–33; due 3–20–34	1–29–34—7 months—B.P. 154/112 Alb. SPT Edema and dyspnea (First trimester normal)	Toxic symptoms continued throughout pregnancy Normal delivery 3–31–34 4–6–34—SPT alb. Clinical diagnosis: probably chronic nephritis	333					—		++	
Case 28 Mrs. C.P. Age 28; IV-para; previous pregnancies normal; last catamenia 7–20–33; due 4–26–34	1–29–34—6 months—B.P. 134/95 Alb. SPT Headaches, dyspnea and edema. Nausea and vomiting for 5 mos.	Albuminuria continued and B.P. increased to 150. Headaches and dizzy spells Delivered 4–29–34 B.P. and urine normal after delivery Clinical diagnosis: toxemia without convulsions	333				±		++±		

S. T., slight trace; S. P. T., slightest possible trace.

March 14, 1934: blood non-protein nitrogen, 120; creatinine, 3.0; uric acid, 5.6; blood pressure 110/80; urinary albumin, none.

Clinical diagnosis: acute nephritis, acute parotitis.

Serum prolan: 66.6 r.u. per 100 c.cm.

Serum estrin: negative with 5 c.cm.

This is the second case (the other is Case 28, ref. 4) definitely diagnosed as nephritic who has shown a normal low prolan. The low estrin is undoubtedly due to the fact that the blood was collected 12 hours after delivery

Case 13. Mrs. M.G., aged 32, II-para. Toxemia had occurred with last pregnancy. Last catamenia was January 20, 1933. Due October 27, 1933. On September 16 at 7½ months her blood pressure was 140/90. There was no edema or urinary albumin. Blood and urine were collected on September 16.

Serum prolan: 200 r.u. per 100 c.cm.

Urinary prolan: 1300 r.u. in 24 hours.

Serum estrin: positive with 3 c.cm.; negative with 2 c.cm.

Urinary estrin: 1500 r.u. in 24 hours.

On October 14 she was admitted to the hospital because of toxemia; blood pressure 150/110, slight trace of urinary albumin, and edema of ankles. Delivery occurred on October 16. Blood was taken on October 15. Clinical diagnosis: toxemia without convulsions.

Serum prolan: 400 r.u. per 100 c.cm.

Serum estrin: negative with 3 c.cm.

This patient showed high prolan and low estrin at 7½ months when clinically only slight hypertension was apparent. A month later, when toxemia was obvious, the serum prolan had risen still higher and its estrin had decreased. The figures for this case confirm the evidence presented by Case 7 that in late pregnancy toxemia, the endocrine imbalance is probably present for some time before definite clinical symptoms become manifest.

Case 14. Mrs. A.M., aged 37 years, VIII-para. All previous pregnancies had been normal. Last catamenia was May 16, 1933. Due February 22, 1934. Patient had diabetes and was on a diet of 1500 calories without insulin. Blood was taken January 29, 1934, at which time she was 8 months pregnant. She had no nausea, headache, eye symptoms, or edema. Blood pressure was 162/110. The urine showed a slight trace of albumin, three plus sugar. Spontaneous delivery occurred on February 12, 1934. Clinical diagnosis: pre-eclamptic toxemia and diabetes.

Serum prolan: 333 r.u. per 100 c.cm.

Serum estrin: positive with 3 c.cm.; negative with 2 c.cm.

The high prolan is consistent with the clinical diagnosis of toxemia. Murphy reported high figures for prolan in the urine of the only two diabetics of his series of pregnant women. However, he gave no figures for serum prolan, did not state the period of gestation when the analyses were made and did not report the progress of the pregnancies. Of Joslin's 89

diabetic women who were followed in pregnancy, 3 developed mild toxemia and one eclampsia. Bowen, quoted by Joslin, found one probable eclamptic in 10 diabetic pregnancies. Doctor Priscilla White, in a recent personal communication, states that among 253 pregnancies in 169 diabetics, eclampsia occurred 7 times and toxemia 5 times. These figures represent an incidence of 2.25 per cent of toxemia and of 4.1 per cent of eclampsia in diabetic women. Williams quotes the frequency of eclampsia in the usual run of pregnancy as less than 1 per cent. It would appear that eclampsia is more common in cases of diabetes.

CASE 15. Mrs. M.F., aged 41 years, IV-para. Previous pregnancies were normal. Last catamenia was November 10, 1933. Due August 17, 1934. Earlier in pregnancy she had had high blood pressure and edema, which had subsided under treatment. She was admitted to the hospital July 26, 1934, with a blood pressure of 230/100, a heavy trace of urinary albumin, and a 17 pound gain in weight in the last 2 weeks. Eye grounds were negative. Spontaneously she went into labor and delivered a living baby on July 27, 1934. Blood was taken while she was in labor. One month after delivery hypertension, edema and albuminuria had completely disappeared. Clinical diagnosis: toxemia without convulsions.

Serum prolan: 200 r.u. per 100 c.cm.
Serum estrin: negative with 5 c.cm.

In this patient the serum prolan, although higher than normal, was not as high as would be expected considering the severity of symptoms. The serum estrin, however, was exceedingly low, and, as was pointed out in our previous paper (4), a quantitative imbalance between these two hormones may be the significant finding in cases of toxemia.

CASE 16. E.M.K., aged 27 years, I-para. She had had no prenatal care. She was admitted to the hospital August 27, 1934, in coma, having had several convulsions. Examination indicated about a 7 months' pregnancy. Blood pressure was 186/118. The urine showed a large trace of albumin with casts, also acetone. She had 3 convulsions after entry. The uterus was contracting regularly on admission. Blood was taken at delivery. Patient was delivered of a macerated fetus August 28 and died August 29.

Blood chemistry: August 28: non-protein nitrogen, 60; urea, 32; uric acid, 7.6; sugar, 153;
August 29: non-protein nitrogen, 75; urea, 41; uric acid, 8.7.

Clinical diagnosis, confirmed by autopsy: eclampsia.

Serum prolan: 1430 r.u. per 100 c.cm.
Serum estrin: positive with 5 c.cm.; negative with 3 c.cm.

Again the prolan and estrin findings in the serum are in keeping with the clinical diagnosis of eclampsia.

In these 9 cases further evidence is found for the assumption that a quantitative endocrine imbalance, due to high levels of prolan and a tendency toward low estrin, is characteristic of late pregnancy toxemia and eclampsia, that this imbalance is present for some time, before symptoms become pronounced (Case 13), and that it is not found in patients whose toxic symptoms are due solely to nephritis (Case 12).

ANALYSES IN THE MIDDLE THIRD OF PREGNANCY ON WOMEN WHOSE CLINICAL PROGRESS HAS BEEN FOLLOWED TO DELIVERY (TABLE II)

Of these 12 women, 7 (Cases 17–22, and 26) had levels of prolan within the limits of normal. Clinically Cases 17, 18, 19, and 20 were normal at the time of analysis and throughout the rest of pregnancy except that Case 20 delivered spontaneously 5 weeks before term. Cases 21 and 26 were nephritic and had normal amounts of prolan. Although she showed some toxic symptoms at the time, Case 22 had normal levels of serum prolan and estrin and her symptoms disappeared soon afterward.

The 5 other women recorded in Table II, Cases 23, 24, 25, 27, and 28, all had excessive serum prolan. Case 23 is the only one of these who showed no toxic symptoms at the time, and she delivered 2 days later, so that what would have happened had pregnancy continued to term is unknown. Case 24, although having an excess of prolan at 6 months, as well as an elevated blood pressure and some edema, showed normal endocrine values 6 weeks later, at which time her toxic symptoms had entirely disappeared. Case 25 had an excess of prolan at the fifth and sixth months. Her hypertension persisted, but she had no other symptoms except a slight trace of albumin once in the seventh month. In Case 27, we find the first exception to the group diagnosed as nephritic. Her hormones were typical

of pre-eclamptic toxemia in spite of a clinical diagnosis of chronic nephritis. It is possible that both conditions were present. Case 28's high prolan at 6 months associated with the symptoms of toxemia is entirely in keeping with the fact that her symptoms persisted and increased and that the clinical diagnosis was toxemia without convulsions.

In this group, therefore, the finding of normal values for prolan and estrin at around the sixth month was followed in every instance by freedom from the symptoms of pre-eclamptic toxemia throughout the remainder of pregnancy. Of the 3 women with a clinical diagnosis of nephritis, 2 had normal prolan and estrin values, while the other showed high prolan. Of the 5 cases whose prolan was high around the sixth month, all but one had a continuation or increase of toxic symptoms until delivery, and this one showed normal values at 7½ months.

SUMMARY

These further quantitative studies of prolan and estrin in 27 additional cases confirm our previous findings of excessive gonad-stimulating hormone and, less consistently, subnormal levels of estrin in the toxemias of late pregnancy and eclampsia. They also indicate that:

1. In normal pregnancy a peak in the level of prolan occurs during the second, third, or fourth month, followed by a marked drop. During the remainder of pregnancy the prolan maintains almost a constant level.

2. The amount of estrin increases as pregnancy advances, reaching a peak at term. There is usually a marked elevation of the estrin level between the third and fifth months.

3. In cases of late pregnancy toxemia an excess of prolan has probably been present for some time before the appearance of toxic symptoms. High levels of prolan during the sixth and seventh months in apparently normal women, therefore, may indicate that toxemia will develop, whereas the finding of normal figures at this time favors the prediction of continued normal pregnancy. A rise after the seventh month may not be significant, since delivery occurs so soon.

4. No abnormal figures for prolan or estrin can be described as typical of miscarriage.

5. The nausea of early pregnancy may be associated with low estrin.

6. Although the highest values for serum prolan yet encountered have been in cases of eclampsia, the degree of excess of prolan does not always run parallel with the severity of the symptoms.

7. Quantitative analyses of serum prolan may be of diagnostic assistance in differentiating between toxemic and nephritic conditions.

8. Quantitative analyses on women who in the middle third of pregnancy are showing some toxic symptoms may be of prognostic value.

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Since this paper was submitted for publication, 12 more pregnant women have been followed from the early months of gestation to delivery. Nine of them were clinically normal throughout and showed typical curves for prolan and estrin. Of the 3 in whom a rise in serum prolan was discovered during the sixth month, 1 had a premature delivery early in the seventh month and the 2 others developed pre-eclamptic toxemia at the eighth month. In 2 of the women who developed no toxic symptoms, the same slight rise in serum prolan as was found in Case 6 (v.s.) appeared after the seventh month.

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THE SYNTHESIS OF HIPPURIC ACID

Its Value in Detecting Hepatic Damage Secondary to Diseases of the Extrahepatic Biliary System[1]

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THE determination of hepatic functional efficiency has become a question of paramount importance, particularly in surgery of the biliary tract. Proper interpretation and treatment of certain complications following operative procedures in this region depend upon a comprehensive understanding of the physiological activities of the liver and the extent of their disturbance by hepatic disease. Though much light has been thrown on several aspects of liver function, many more remain obscure. Therefore, various complications following operations on the biliary tract still challenge the investigator for a satisfactory explanation.

Recently, Dr. William L. Estes, Jr., called our attention to a rather troublesome complication arising in 4 patients following operation for common duct obstruction in his service at St. Luke's Hospital. These patients had recovered favorably from the initial reaction, but on the second or third day the usual postoperative nausea failed to subside. The continued nausea was associated with occasional vomiting, loss of appetite, and great weakness. In spite of early treatment with the Jutte tube and other measures, these symptoms persisted for 2 or 3 weeks, leaving the patient in a toxic debilitated condition; 1 of the patients even became drowsy and then semistuporous. None of the operations were technically difficult and aside from a high icteric index and a moderate degree of hepatitis, there was no other indication of hepatic disturbance out of the ordinary. Although all patients were finally relieved, following the administration of glucose intravenously, the cause of their symptoms was obscure. It was assumed, however, that noxious substances were being absorbed from the gastro-intestinal tract, with a concomitant impairment of the detoxifying function of the liver.

The urgent desire to solve this problem prompted an investigation of practically all cases with disease of the biliary tract in this clinic from October 1, 1933, to April 1, 1934. The liver was studied from the aspect of its detoxifying power, the method of Quick being used(16): the synthesis of hippuric acid recently introduced by him as a new test of liver function. The test was utilized not only because it seemed to offer a possible solution for the problem, but also, to demonstrate its value in disclosing hepatic damage secondary to diseases of the gall bladder and biliary ducts.

The synthesis of hippuric acid constitutes a detoxifying process brought about by the introduction of benzoic acid into the organism and its subsequent conjugation with glycine. The fate of ingested benzoic acid has been quite extensively studied in man and in various animals, in an effort to explain the chemical changes involved and the site of synthesis of hippuric acid. Benzoic acid ingested by man is combined with glycine and eliminated in the urine almost completely as hippuric acid, except, perhaps, for a small portion which may be combined with glycuronic acid and eliminated as glycuronic acid monobenzoate(12).

Though Lachner, Levinson, and Morse first suggested that hepatic disease disturbs the synthesis of hippuric acid, little attempt had been made prior to the work of Quick (15, 16) to apply the synthesis for the detection of hepatic damage in man. The only previous work showing a reduction in the output of hippuric acid in man with hepatic involvement was that of Bryan. The earlier work of Bunge and Schmeideberg rather conclusively established that in the dog the synthesis occurs only in the kidney. Quick(13) has recently confirmed the original work of Bunge and Schmeideberg in the dog, but in the rabbit he found, as did Friedmann and Tachau, that the liver partakes in the synthesis. He believes that in man, as in the rabbit, the syn-

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thesis also occurs in the liver(16). Quick(12) has shown that the organism has no store of preformed glycine and the rate of synthesis of hippuric acid is governed by the ability of the organism to produce glycine. Also, the organism has a definite maximum capacity to produce this substance, for regardless of the amount of benzoic acid taken in, the hourly output of hippuric acid (in the absence of exogenous glycine) remains relatively constant. Since glycine is generally considered to be synthesized in the liver, it was thought that certain types of liver damage might disturb the synthesis and result in a diminished output of hippuric acid.

The present investigation on the excretion of hippuric acid was in a group of 44 cases. Although primarily concerned with liver damage secondary to diseases of the extrahepatic biliary system, our interest spread so that a few cases with other pathological involvement of the liver were also studied. Ten subjects, clinically free of hepatic and renal disease, were used as control cases to establish the normal output of hippuric acid. Twenty-seven cases had diseases of the gall bladder and bile passages, of which 26 were inflammatory and 1 was carcinoma. All cases, excepting one of catarrhal jaundice, came to operation or autopsy. The excretion of hippuric acid was compared with the gross pathological findings and, when possible, with other liver function tests of more established significance. There were also 3 cases of carcinoma, 3 of cirrhosis, and 1 of chronic passive congestion of the liver. Two of the 3 cases of carcinoma were discovered at operation and the test was run subsequently to determine the rate of excretion of hippuric acid and to compare the result with the bromsulphalein test.

The technique followed was identical with that outlined by Quick (15, 16) in his "Simple Clinical Method" as follows:

Five and nine-tenths grams of sodium benzoate dissolved in 30 cubic centimeters of water is administered 1 hour after breakfast consisting of coffee and toast. The patient is then given a half glass of water. Immediately after taking the drug the patient voids, and then collects complete hourly specimens for 4 hours. These are preserved with toluene, and hippuric acid determined in each specimen. Each hour specimen is measured, transferred to a small beaker and acidified with concentrated hydrochloric acid until acid to congo red; 1 cubic centimeter of the acid is usually sufficient. The solution is vigorously stirred until the precipitation of hippuric acid is complete, and then is allowed to stand for 1 hour at room temperature. The precipitate is filtered off on a small Buchner filter plate, washed with a small quantity of cold water, and allowed to air dry. The hippuric acid thus obtained is either weighed (to the second decimal place, which is usually sufficient) or titrated with two-tenths normal sodium hydroxide, phenolphthalein being used as indicator. To obtain the total hippuric acid one must add to the amount thus obtained the calculated quantity remaining in solution; 100 cubic centimeters of urine will dissolve 0.33 gram of hippuric acid. In case a specimen exceeds 125 cubic centimeters it should be slightly acidified with acetic acid and concentrated on the water bath to about 50 cubic centimeters before precipitating the hippuric acid. The results are best expressed in terms of benzoic acid. To convert hippuric acid to benzoic, one multiplies by 0.68. In normal adults the output of benzoic acid as hippuric acid is approximately 1 gram or more during the second and third hours and the total for 4 hours is from 3 to 3.5 grams.

TABLE I.—EXCRETION OF HIPPURIC ACID IN NORMAL SUBJECTS*

Subject	1 hour	2 hour	3 hour	4 hour	Total
1	0.63	0.98	0.78	0.77	3.16
2	0.60	0.92	1.07	0.75	3.34
3	0.54	0.87	1.01	0.64	3.06
4	0.82	1.01	1.20	0.43	3.46
5	0.77	1.05	0.96	0.76	3.54
6	0.82	1.05	0.99	0.42	3.28
7	0.38	0.61	1.13	0.86	2.98
8	0.41	1.02	0.73	0.87	3.03
9	0.51	0.69	0.97	1.02	3.19
10	0.44	0.93	1.08	0.68	3.13

*Hippuric acid in terms of benzoic acid in grams.

Two cases were given glycine, to observe the effect of this substance on reduced hippuric acid excretion in hepatic disease. Five grains, three times a day, was administered 2 days before repeating the test.

The results obtained in this investigation show that the excretion of hippuric acid rather consistently bears out the condition of the liver. The excretion in the 10 control cases was 1 or more grams for the second and third hours and ranged from 2.98 grams to

TABLE II.—EXCRETION OF HIPPURIC ACID IN DISEASES OF THE BILIARY TRACT

Case and age	Duration of symptoms	Icteric index	Vandenberg direct indirect—mgm. bilirubin per 100 c.cm. of blood	Bromsulphalein per cent of dye remaining after injection	Hippuric acid in terms of benzoic acid in grams					Diagnosis, pathological findings, result
					1 hr.	2 hr.	3 hr.	4 hr.	Total	
1 J.A. 45	3 yrs.	6	Direct: delayed positive; indirect: 0.4 mgm.		0.65	0.99	0.88	0.64	3.16	Chronic cholecystitis. Liver appeared normal. Uneventful recovery
2 S.K. 65	7 yrs.			20% after 15 min., 0% after 60 min.	0.41	0.93	1.10	0.84	3.28	Chronic cholecystitis with lithiasis. Liver appeared normal. Uneventful recovery
3 E.S. 33	11 yrs.	4			0.70	0.99	1.10	0.34	3.13	Chronic cholecystitis. Liver appeared normal. Uneventful recovery
4 A.P. 44	2 yrs.	6			0.68	0.92	1.01	0.63	3.24	Chronic cholecystitis. Liver appeared normal. Uneventful recovery
5 J.S. 29	3 yrs.	6			0.71	0.73	0.78	0.76	2.98	Chronic cholecystitis. Liver appeared normal. Uneventful recovery
6 J.M. 30		3		35% after 10 min., 10% after 60 min.	0.96	0.86	1.30	0.28	3.40	Chronic cholecystitis with lithiasis. Liver appeared normal. Uneventful recovery
7 J.S. 58	5 yrs.	7		25% after 30 min., 0% after 60 min.	0.52	0.87	0.99	0.64	3.02	Chronic cholecystitis with lithiasis. Liver appeared normal. Uneventful recovery
8 S.P. 44	2 yrs.	2	Direct: delayed negative; indirect: 0.2 mgm.		0.71	0.93	1.14	0.46	3.24	Acute cholecystitis. Liver appeared normal. Uneventful recovery
9 M.M. 55	7 yrs.	35			0.28	0.72	0.83	0.20	2.03	Chronic cholecystitis with lithiasis. Common duct obstruction. White bile. Marked hepatitis and fibrosis. Uneventful recovery
10 G.A. 48	2 yrs.	5			0.17 0.25 0.23	0.59 0.53 0.45	0.61 0.64 0.53	0.44 0.65 0.64	1.81 2.07* 1.85†	Chronic cholecystitis with lithiasis. Half of gall bladder gangrenous. Cholangitis. Marked hepatitis and fibrosis. Convalescence stormy
11 M.K. 41	6 mos.	10		20% after 15 min., 10% after 60 min.	0.26	0.51	0.73	0.54	2.04	Chronic cholecystitis. Liver appeared smaller than normal. Slight fibrosis. Spleen markedly enlarged. Uneventful recovery
12 L.A. 46	1 yr.	4			0.23	0.55	0.72	0.49	1.99	Chronic cholecystitis with lithiasis. Marked hepatitis and fibrosis. Uneventful recovery
13 J.M. 23	1 yr.	2			0.28 0.43	0.60 0.74	0.68 0.63	0.39 0.56	1.95 2.36†	Chronic cholecystitis. Marked hepatitis and fibrosis. Uneventful recovery
14 J.D. 43	2 yrs.	4			0.17	0.89	0.83	0.38	2.27	Chronic cholecystitis with lithiasis. Liver enlarged. Gall bladder perforated, markedly thickened and gangrenous. Marked fibrosis and hepatitis. Uneventful recovery
15 M.S. 33	1 yr.	2			0.24	0.18	1.36	0.90	2.68	Chronic cholecystitis with lithiasis. Moderate amount of hepatitis and fibrosis. Uneventful recovery
16 M.R.	1 mo.	12	Direct: immediately positive; indirect: 1.5 mgm.		0.80	0.54	0.54	0.64	2.52	Chronic cholecystitis with lithiasis. Liver enlarged with considerable fibrosis. Wassermann negative
17 Y.P. 38	6 mos.	2			0.65	0.77	0.80	0.69	2.91	Chronic cholecystitis with lithiasis. Liver slightly enlarged. Mild hepatitis. Uneventful recovery
18 S.S. 65	1 yr.	10	Indirect: 0.6 mgm.		0.41	0.43	0.67	0.52	2.03	Chronic cholecystitis with lithiasis. Stones in common and hepatic ducts. Partial obstruction. Marked hepatitis and fibrosis. Uneventful recovery
19 J.E. 44	3 yrs.				0.40	0.99	0.98	0.53	2.90	Chronic cholecystitis with lithiasis. Mild hepatitis, otherwise liver appeared normal. Stones in common duct. Uneventful recovery

*Glycine administered.
†Two weeks after operation, standard technique.

TABLE II.—EXCRETION OF HIPPURIC ACID IN DISEASES OF THE BILIARY TRACT—Continued

Case and age	Duration of symptoms	Icteric index	Vandenberg direct indirect—mgm. bilirubin per 100 c.cm. of blood	Bromsulphalein per cent of dye remaining after injection	Hippuric acid in terms of benzoic acid in grams					Diagnosis, pathological findings, result
					1 hr.	2 hr.	3 hr.	4 hr.	Total	
20 J.R. 43	4 yrs.	5		20% after 30 min., 10% after 60 min.	0.08 0.15	0.07 0.28	0.38 0.46	0.50 0.34	1.03 1.23*	Chronic cholecystitis with lithiasis. Marked hepatitis and fibrosis. Stormy convalescence
21 E.Y. 33	3 yrs.	60	Direct: immediately positive; indirect: 10.0 mgm.		0.49	0.81	0.86 (1.0–9–33)	0.64	2.80	Acute exacerbation of chronic cholecystitis and lithiasis. Stone in common duct. Liver palpable. (Clinical diagnosis)
21 E.Y. 33	3 yrs.	2	Direct: delayed positive; indirect: 0.2 mgm.		0.31	0.63	0.89 (2–18–34)	0.92	2.75	Chronic cholecystitis with lithiasis. Stone in common duct. Gall bladder greatly thickened. White bile. Cholangitis. Extensive hepatitis and fibrosis. A large number of stones had eroded through the anterior wall of the gall bladder and had become encapsulated in the substance of the liver. Uneventful recovery
22 E.S. 70	3 mos.	50			0.20	0.14	0.09	0.09	0.52	Carcinoma of the gall bladder with metastasis to the liver. (Autopsy)
23 S.C. 56	1 yr.	4			0.22	0.95	0.89	0.58	2.64	Chronic cholecystitis with lithiasis. Liver slightly enlarged. Moderate amount of fibrosis. Uneventful recovery
24 M.S. 56	1 yr.	12		60% after 30 min.	0.44	1.03	0.23	0.49	3.19	Chronic cholecystitis with lithiasis. Slight hepatitis, otherwise liver appeared normal. Uneventful recovery
25 J.D. 35	8 yrs.	3	Direct: delayed positive; indirect: 0.8 mgm.		0.82	0.87	1.10	0.31	3.10	Chronic cholecystitis with lithiasis. Stones in common and hepatic ducts. Marked hepatitis and fibrosis. Died 25 days after operation from cardiac decompensation
26 H.S. 20		20	Direct: immediately positive; indirect: 1.5 mgm.		0.34	0.51	0.40	0.42	1.67	Catarrhal jaundice. (Clinical diagnosis)
27 A.F. 40					0.85	0.99	0.79	0.48	3.11	Cholecystectomy 1 year ago—(2–1–33) (Chronic cholecystitis with lithiasis, mild fibrosis.) Admitted for pain in epigastrium 3–5–34. Discharged improved

*Glycine administered.
†Two weeks after operation, standard technique.

3.54 grams for the total of 4 hours. Table I confirms Quick's (16) findings as the normal output for adults.

The excretion of hippuric acid was found to be within normal limits in biliary tract disease where the liver appeared normal (Table II, Cases 1 to 8, inclusive). A definite inhibition was noted in practically all cases presenting gross structural changes of the liver (Cases 9 to 23, inclusive). Generally, the degree of inhibition corresponded to the amount of hepatic damage. The only exception was in Case 25, which produced a normal output in the presence of marked structural change of the liver, and in Case 24 with only a slight involvement. The bromsulphalein test in Case 24, however, was out of proportion to the amount of apparent hepatic damage. A uniformly lowered output was observed in biliary obstruction, Cases 9, 11, 16, 18, 21, and 22. Case 22, with obstruction due to gall bladder carcinoma, yielded the low result of 0.52 gram benzoic acid as hippuric acid excreted in 4 hours. Case 21 illustrates Quick's (16) observation, that the clearance of jaundice does not necessarily mean the liver has returned to normal. The patient, at the height of jaundice, excreted 2.80 grams benzoic acid as hippuric acid, while 4 months later after complete disappearance of jaundice, the excretion was 2.75 grams. Case 26 of catarrhal jaundice registered a decidedly low output.

TABLE III.—EXCRETION OF HIPPURIC ACID IN CARCINOMA, CIRRHOSIS, AND CHRONIC PASSIVE CONGESTION OF THE LIVER

Case and age	Duration of symptoms	Icteric index	Bromsulphalein per cent of dye remaining after injection	Hippuric acid in terms of benzoic acid in grams					Diagnosis, pathological findings, result
				1 hr.	2 hr.	3 hr.	4 hr.	Total	
A.K. 45	6 mos.		20% after 20 min.	0.37	0.44	0.97	0.78	2.56	Atrophic cirrhosis. Discharged improved. (Clinical diagnosis)
J.C. 56	6 mos.	1		0.12	0.29	0.61	0.32	1.34	Cirrhosis of the liver with ascites. Discharged improved. (Clinical diagnosis)
L.S. 37	1 yr.	4	50% after 40 min.	0.25	0.39	0.53	0.41	1.58	Chronic passive congestion. Liver markedly enlarged. (Clinical diagnosis)
L.S. 58		1	30% after 30 min., 30% after 60 min.	0.76	0.52	0.81	0.76	2.85	Carcinoma of liver (metastatic?). Liver somewhat enlarged and surface studded with carcinoma nodules. Discovered accidentally while exploring the abdomen during the repair of a large umbilical hernia
M.M. 56	2 yrs.		50% after 30 min., 40% after 60 min.	0.27	0.60	0.64	0.57	2.08	Carcinoma of liver (metastatic) from carcinoma of rectosigmoid. Liver slightly enlarged, entire surface studded with secondary nodules. (Diagnosis laparotomy). Permanent colostomy
M.C. 60	6 mos.			0.19	0.34	0.41	0.51	1.45	Carcinoma of liver (metastatic?). Liver palpable, large nodular mass in epigastrium corresponding with left lobe of liver in a patient with scirrhous carcinoma of right breast with metastasis to axilla. (Diagnosis of liver involvement clinical)
C.B. 49	3 mos.?	7	45% after 30 min.	0.45	0.71	0.71	0.66	2.53	Hypertrophic cirrhosis. (Clinical diagnosis)

Except in Cases 24 and 25 the hippuric acid test seemed to be more accurate than the bromsulphalein test in foretelling the condition of the liver.

A diminished excretion also resulted in carcinoma, cirrhosis, and chronic passive congestion of the liver (Table III). The bromsulphalein test also indicated extensive damage in this last group of cases.

The second line of figures in Cases 10 and 20, Table II, indicates that the excretion of hippuric acid depressed by hepatic disease is slightly but definitely increased following the administration of glycine. The excretion again diminished when glycine was withdrawn, as shown by the third line of figures in Case 10.

EVALUATION

The test is contra-indicated in nephritis with nitrogen retention, because the behavior of hippuric acid is not unlike other nitrogenous excretory products(16). Another disadvantage is that the sodium benzoate is sometimes vomited. Three cases were encountered in this study that could not be subjected to the test because the sodium benzoate was repeatedly vomited.

The manifold duties of the liver, with its remarkable power of regeneration and functional reserve, constitute a great obstacle in the accurate determination of hepatic efficiency. However, as pointed out by Quick (16), "it must not be forgotten that various functions of the liver are not distinct and independent, but closely interrelated, so that an injury to one may affect several others as well. Certain mechanisms of the liver are so delicate, that there is practically no margin of safety."

Glycine is not only involved in the detoxication of benzoic acid but also, a supply is necessary in the synthesis of glycocholic acid (8). Glycocholic acid, most prominent bile acid in human bile, is formed by the union of cholic acid with glycine. It is reasonable to assume, therefore, that the mechanism effecting the conjugation of benzoic acid with glycine, to form hippuric acid and the one affecting the conjugation of cholic acid with glycine to form glycocholic acid are similar. The latter being a normal physiological process, perhaps, utilized incidentally to rid the body of a noxious substance. The synthesis of glycine seems to have little reserve, for the diminished excretion of hippuric acid in catarrhal jaundice is out of proportion to the amount of hepatic damage (15, 16). Also, Smyth and Whipple, found that a dose of

chloroform insufficient to produce any demonstrable change in the liver cells, caused a definite decrease in the excretion of bile acids. This related functional disturbance may again be demonstrated clinically. Green, Walters, and Frederickson have shown that in biliary obstruction, the formation of bile acids is greatly depressed. The same condition in the present investigation shows in agreement with both Bryan and Quick, a diminished output of hippuric acid.

The influence of benzoic acid and glycine on the excretion of uric acid is interesting. Lewis and Karr were first to observe that the ingestion of benzoic acid decidedly depressed the excretion of uric acid. This finding was confirmed by Swanson, who found that there was not only a marked decrease in the uric acid content of the urine but also an increase in the uric acid content of the whole blood and plasma. The ingestion of glycine on the other hand, according to Lewis, Dunn, and Doisy, more recently to Christmann and Mosier, is followed by an increased excretion of uric acid. Quick (12, 14) finds also that glycine "like other glycogenetic amino acids not only stimulates the excretion of uric acid but also prevents and counteracts the depressing action of benzoic acid." Bruhl doing microscopic studies on the glomerular circulation in the frog found that the circulation stops when there is a lack of glycine. Watzadse previously had made similar observations. In the light of these observations, it seems that glycine has a definite stimulating action on kidney function.

It would seem probable, therefore, that hepatic damage disturbing the synthesis of glycine may exert a depressing action on kidney function. On this basis might be explained the type of "liver death" which has been cited by Heyd with manifestations of renal involvement.

SUMMARY AND CONCLUSION

The results obtained in the present study show:

1. The excretion of hippuric acid in normal subjects was one or more grams for the second and third hours and a total of 2.98 to 3.54 grams for 4 hours.

2. The excretion was diminished in diseases of the extrahepatic biliary system, presenting gross structural changes of the liver. Obstructive jaundice registered a uniformly lowered output. Generally, the inhibition was governed by the amount of damage.

3. Hepatic damage from carcinoma, cirrhosis, and chronic passive congestion, also gave a reduced output.

4. Excretion of hippuric acid reduced as a result of hepatic disease was slightly increased by the administration of glycine.

5. A similar complication alluded to previously was not encountered, though two cases, 10 and 20, Table II, with mild manifestations and of shorter duration, had a decidedly low output.

From these observations it is concluded that the hippuric acid test is a method of considerable merit not only to disclose but also to give an approximate amount of structural hepatic damage resulting from diseases of the biliary tract. It also is of value in detecting hepatic damage from other pathological involvement of the liver.

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DYSONTOGENETIC AND MIXED TUMORS OF THE UROGENITAL REGION

With a Report of a New Case of Sarcoma Botryoides Vaginæ in a Child, and Comments Upon the Probable Nature of Sarcoma

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In 1908 a case of infantile vaginal botryoid tumor came under observation, and so interested me on account of its peculiar appearance, rapidly fatal course, and evident rarity that I reported it.[1]

Some ten years later, in conversation with Dr. Joshua L. Sweet, I mentioned the case, and suggested that it probably had its origin in a defect of embryonal development, when to my surprise, he remarked that he was sure it had, and that, although I had discovered no evidence of the fact, it was really a "mixed tumor," belonging in the same class as those about which he had written his "Inaugural Dissertation" for the degree of Doctor of Medicine at the University of Giessen, in 1901. I was embarrassed to think that I had overlooked his dissertation; but when he, later, kindly presented me with a copy, I understood why. My literary research had been concentrated upon the subject of sarcoma, and his paper was entitled "Die Mischgeschwuelste am unteren Ende des Urogenitalapparates der Kinder." Ten more years were to pass before opportunity to revive the subject arrived in the form of a specimen and case report sent by Dr. A. P. Condon of the Nicholas Senn Hospital in Omaha, Nebraska, with permission to publish the case if it proved to be sufficiently interesting. The following is the protocol:

N. J., a little girl 6 years of age came to the hospital, January 15, 1932, with a small cystic polypoid tumor mass growing from the anterior wall of the vagina and projecting from the vulva. It was excised, and a treatment of 600 milligram hours of radium administered. But in about 2 months the patient was back again, with a recurrence covering about 2 inches of the right wall of the vagina, and made up of an aggregation of small cyst-like masses. These were also excised, the bases curetted, and a treatment of 1200 milligram hours of radium applied by inserting the agent deeply into the tissues. This also failed, and in January, 1932, when the patient was again seen, a large recurrent mass almost completely filled the vagina. As the repeated excisions, supplemented by the use of radium, had failed, further treatment was not urged, although the tumor seemed to be localized in the vagina, the finger in the rectum failing to find anything in the pelvis.

From this time on the patient's condition became steadily worse, and the attending physician describes what subsequently happened, as follows:

The vaginal mass distended the vulvar opening to what seemed to be the extreme limit, causing pressure necrosis of the skin margins, which became

[1] Am. J. M. Sc., 1911, 141: 570.

covered with heavy crusts. The urethral orifice disappeared from view, the urine escaping between the lobes of the tumor. There was, however, no considerable retention, the patient always being able to void the urine. The external portion of the tumor seemed to break down, diminishing in size and becoming covered with a heavy crust; the internal portion, which was easily palpated, extended to about an inch below the umbilicus and some 2.5 inches to the left. The pelvic pressure seemed to cause contractures of the legs that were tightly drawn up upon the abdomen. The rectum seemed to have perforated about 4 weeks before death, which took place on November 15, 1932.

The necropsy was performed at the home of the patient, in a small town in Nebraska, by the family physician, who was kind enough to furnish the following details:

The pelvis was eviscerated, the tumor, the rectum, the uterus, the vagina, and the ovaries being removed in one large partly amalgamated mass. Casual examination of the liver, kidneys, spleen, and vermiform appendix, revealed nothing abnormal. The thorax and cranium were not opened.

The removed mass of pelvic contents was placed in a jar of formaldehyde and later forwarded to me. It is unfortunate that the tissues could not have been more carefully examined in the fresh condition, as the formaldehyde not only firmly fixed them in a position of considerable distortion, but also rendered them very brittle. This is what I found:

The general tissue mass measures 15 by 10 centimeters, and consists principally of neoplastic tissue, whose lower part, about as large as a good sized orange, lobulated, incrusted, necrotic, and made up of alternating soft and firm substance, is probably that which protruded through the vulvar orifice during life (Fig. 1). Except for a short and narrow strip of wrinkled skin, supposed to be from one of the labia, nothing can be definitely identified as belonging to the external genitalia. The evisceration was evidently performed through the abdominal opening, and the attachments cut away from the inside. Most of the urethra has become amalgamated with the tumor mass, and the meatus has been lost through ulceration. About 8 centimeters of compressed rectum is loosely attached to the left side of the mass, through which its lower part passes to open in a deep fissure on its inferior posterior surface.

The presence of a small quantity of fecal matter throughout its whole length shows that although compressed into a flattened ribbon, the rectum was patulous, and the suspected rupture had not occurred. Except for a very limited extent in the immediate neighborhood of the anus the rectum escaped invasion by the tumor. The vagina is so altered as to be scarcely recognizable. It is 7 centimeters in length and 6 centimeters in width, and when divided longitudinally (Fig. 2), is found to contain a large irregular space with surrounding walls which vary from one-half to 2 centimeters in thickness. The tissue of these thickened walls must have been very soft and necrotic, but after fixation in the formaldehyde, crumbles away, leaving a curious appearance resembling a tangled mass of pale colored slender worms—probably thrombosed blood vessels.

The uterus, broad ligaments, and ovaries (Fig. 3) are pushed up and to the left, the body of the uterus being anteflexed and its anterior surface adherent to the bladder.

There are a number of flattened neoplastic discs in the broad ligament of the right side, and on the peritoneal surface of the uterus and both ovaries, representing lymphatic metastasis or local extension of the tumor by permeation. Whether there may have been metastasis to the lungs, can never be known as the necropsy did not include the opening of the thoracic cavity.

The upper anterior vaginal wall is completely amalgamated with the neck and posterior wall of the bladder to form a tumor mass 4 centimeters in thickness, projecting into the bladder from behind, and almost completely filling it (Fig. 2). Faint striations, caused by the survival of some of the normal structures in the midst of the general neoplastic mass, indicate the original limits of the bladder and vagina.

Some well preserved parts of the tumor present a finely fasciculated appearance, others are homogeneous. The color, changed by fixation, is pale grayish yellow, and the consistence is firm, though the impression cannot be escaped that it was originally very soft, and probably edematous. But it is neither cystic nor hemorrhagic. The softer parts, upon section, show no other explanation for their softness than a looser texture that may have been due to edematous infiltration.

MICROSCOPY

I began the histological study of my first case (1911) with the clinical diagnosis of sarcoma botryoides vaginæ already made, expected the microscope to show sarcoma, and, though finding it atypical, persisted in regarding it as sarcoma. But during the interval of 20 years my ideas had changed and my approach to the present case was correspondingly different: I was now looking for evidences by which to prove that the lesion was a "mixed tumor."

I have carefully reviewed the old sections made from the tissue of the first tumor, and am certain that were I seeing them for the first time, and without my present preconvic-

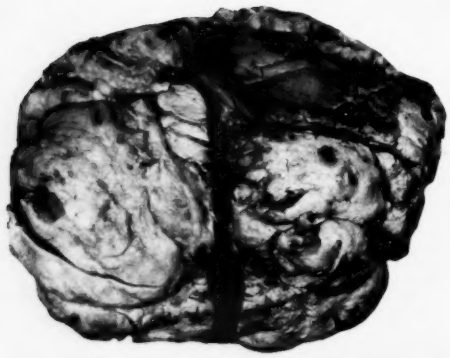

Fig. 1. This shows (⅔ natural size) a front view of the tumor mass that projected through the vulvar opening. The perpendicular separation is our incision through the entire tissue mass. The lateral lines were natural separations between lobules of the tumor.

tion that it was a "mixed tumor," I should again reach the conclusion of 20 years ago, and describe it as an edematous, and probably myxomatous, spindle cell sarcoma (Botryoid sarcoma).

Sections made from the various blocks of tissue taken from the present tumor were very disappointing in their simple histology. The fundamental structure was an edematous (myxomatous?) delicate fibrillar tissue much resembling that of a nasal polyp. Some areas contained relatively few, and inactive cells, others a greater number of cells, some of which were mitotic, while still others were composed entirely of cells with hyperchromatic and mitotic nuclei (Fig. 4). The cells, for the most part, were long delicate spindles, though here and there one encountered shorter spindles, and occasional areas of what seemed to be round cells. Near the surfaces there was much necrosis and ulceration with characteristic inflammatory cellular infiltrations. Again the histology served to warrant the diagnosis of spindle cell sarcoma.

But the sections cut from a block of tissue taken from the part mentioned as showing a strip of skin supposed to represent one of the labia presented some elements that should not be overlooked and may be significant.

Below the skin, which was well preserved, and free from neoplastic infiltration, though its corium was infiltrated with inflammatory cells, the tissue became edematous, and tumor cells, nearly all long slender spindles, began to appear. Among them were occasional giant cells that seemed to be of two kinds. Those nearest to the surface were usually of rounded shape, and resembled foreign body giant cells, which they probably were, while some of those more deeply situated were elongated, the most deeply situated, among the tumor cells, very long, with the nuclei sometimes collected near the poles, sometimes distributed along a band of cytoplasm of uniform width and pronounced eosinophilic reaction. Some of these giant cells resembled the disturbed sarcous elements observed in injured and supposedly regenerating voluntary muscle. It seemed as though they might be rhabdomyoblasts, whose transformation into striated muscle fibers had been checked through the occurrence of the edema, necrosis, and infection. Hundreds of them were examined in the hope of finding some that might show striations but without success. Further study of other slides from other parts of the tumor, showed occasional similar cells and cylindrical nucleated bands of fibrils, eosinophilic in reaction, but without cross striations (Fig. 5). In the published illustrations of sections of other tumors, elements appear very similar to those just described except that some among them were striated. Making allowance for the embryonal and diseased condition of the tissue, it seems reasonable to assume that the cells under consideration may have been embryonal muscle cells, and that the tumor was a mixed tumor (rhabdomyoma), though it is impossible to prove it.

From the clinical and morbid anatomical points of view, there is no doubt but that my first and second tumors are identical, and it is probable they both belong among the "mixed tumors" referred to by Sweet and many others. But without the presence of indubitable muscular or cartilaginous elements or some other positive evidence of heterologous structures could they be correctly called mixed tumors? We shall return to this question later; for the present let the term "mixed tumor" be set aside and the lesions designated, as Schwalbe has suggested, "dysontogenetic tumors."

Thus freed from the limitations necessitated by nomenclature, and abandoning the idea that the dysontogenetic tumors must be "botryoid" or "sarcomata" or "mixed tumors," I next set about collecting all of the tumors reported in the literature whose apparent origin, clinical peculiarities, anatomical distribution, or histological structure made it probable that they might be of use in forming an intelligent understanding of their own nature and origin, as well as that of the whole group. A lengthy bibliography was thus assembled. Of the total of 516 references collected, 41 were not available, but 475 contributions were actually examined, and as many as seemed worth while were read.

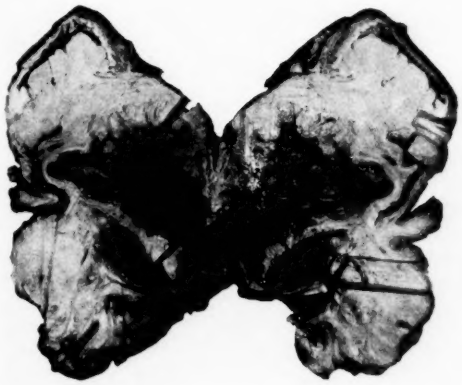

Fig. 2. Complete section through the entire tumor mass (⅓ natural size) showing the bladder with its inferior posterior wall destroyed by the tumor mass that projected into and nearly fills it; the middle part of the urethra whose meatus cannot be seen because it opens into a sulcus on the other side of the tumor; the vagina whose entire wall is invaded, thickened, and internally necrotic so as to result in an irregular space with a shaggy appearance as though studded with slender worms (thrombosed vessels); the rectum, slightly flattened by pressure, but patulous, and undisturbed by tumor invasion; the large mass that projected through the vulvar opening.

Fig. 3. View of the tumor mass and adjacent viscera as seen from the intra-abdominal surface (½ natural size). It shows the uterus anteverted and anteflexed and bound to the bladder, with tumor nodules upon its fundus. The ovaries, one small and dark colored, the other pale, enlarged and the seat of a peripheral metastasis.

Of this literature it was soon discovered that a considerable portion, consisting of reports of tumor cases hurried into the literature shortly after operation, and before either the histopathological examination revealed their nature, or the subsequent clinical history showed whether they were malignant or not, was of very little value. Moreover, it contains many cases in which the identification of the tumors was either entirely wrong or very doubtful (endotheliomata, etc.), and deals with the transformation of benign into malignant tumors (fibroids to sarcomata) as though such a change were a demonstrated and accepted fact.

A bewildering terminology, containing 119 different names, gradually built up, also made it extremely difficult to trace the dysontogenetic tumors through the literature as one did not know under what headings to seek for them.

But the result of these studies has been as fruitful as it has been interesting. Among the dysontogenetic tumors of the urogenital region, with which this paper has to do, many of which are distinctly mixed tumors, there is a great divergence of appearance and structure. Many are very soft, edematous, myxoid, polypoid, and cystic—"botryoid"—while others are firm, dense, fibroid, muscular, cartilaginous, or even osseous. The extremes in the series appear to be entirely different types of tumors and, indeed, they are, as can be inferred from the numerous terminology. A "myxoma" is certainly not the same tumor as a "chondroma." It is not the quality of the tumor, but its mode of origin that makes it dysontogenetic. Many suppose that the very soft, botryoid tumors constitute a variety *sui generis*, but the botryoid or "grape-like" appearance only results from the amount of moisture the tumor happens to contain. Tumors of similar histological structure are sometimes dense and dry.

It has been thought that the botryoid tumors are peculiar to infancy, or at least to early childhood. But Kaschewarowa-Rednewa observed one at 15, and another at 17 years of age; Steintahl one at 22 years of age and beginning with Spiegelberg, whose patient was 45 years of age, many cases have been reported in the fifth and sixth decades of life, Robertson having seen one at 69 years of age.

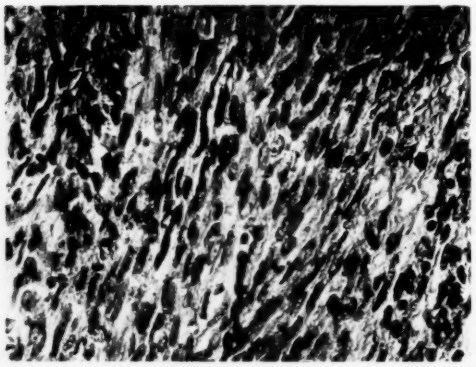

Fig. 4. Details of the structure of one of the densest and most cellular parts of the tumor, showing the spindle cell structure usually called "sarcoma."

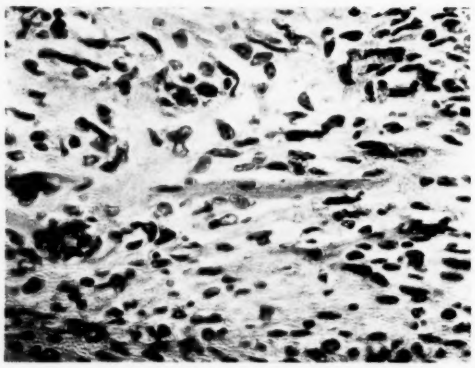

Fig. 5. Details of one of the softer parts of the tumor, with two of the elongated eosinophilic structures thought to be muscle fibers, though none showed cross striations.

Dysontogenetic tumors have been observed to project as a small strawberry-like mass from the urethra or vagina at the time of birth; to project into the bladder, either from its walls, or from the prostate, to grow in the vesico-vaginal septum, extending into the bladder or into the vagina; from anterior wall of the vagina, either high up or low down, in either case eventually filling the cavity of the viscus with the tumor mass; from the posterior wall of the vagina; from the anterior lip of the cervix uteri; from the endometrial tissue of the cervix or fundus of the uterus, or to occur as complications of uterine fibroids.

Some of the tumors make their appearances at fairly well defined ages. The botryoid tumors of the vagina are overwhelmingly more frequent in early childhood than at any other time, while the similar tumors of the uterus occur chiefly in later life. Seventy-four of the reported cases of botryoid vaginal tumors occurred in the first 22 years of life, and none thereafter, while of the similar uterine tumors, only 22 were reported during the first 22 years of life, and 39 thereafter. Forty-two of the vaginal tumors were found in children of 2 years or less, against 5 uterine tumors of the same kind. Similar soft tumors of the bladder and prostate are almost peculiar to childhood.

ETIOLOGY

To understand what is here meant by "dysontogenetic" tumors, and why so many different varieties and seemingly unrelated tumors are brought together and treated as though the same, it is necessary to recall the embryology of the parts concerned.

At a very early stage of development, when the yolk sac is being converted into the primitive intestine, the allantois is given off as a diverticulum, rapidly grows to a considerable size, and appears as a sac connected with the primitive gut by a tubular stalk that soon parallels the growing omphalomesenteric duct, and ultimately becomes united with it to form the belly stalk of the growing embryo. Later the intra-embryonal part of the allantois becomes dilated into a fusiform sac, the office of which seems to be to receive the excrementitious products of the primitive urinary organs, the pronephros (?) and metanephros. At about the same time the pronephric ducts cease to be connected with the tubules of the pronephros, and become the ducts of the more important mesonephros, and as that organ progresses in its development, grow caudally to open into the expanded part of the allantois, now the urogenital sinus. At a slightly later date, on each side of the body, along the genital ridge, a fold of tissue curls inward to form a tube, the upper end of which remains open with a flaring trumpet-like expansion, while the lower part closes over to form a cylindrical tube, the muellerian tube, that elongates caudally descending toward the urogenital sinus where the approximated terminations

of both cause a slight projection in the posterior wall of the sinus, called the muellerian tubercle. These tubular terminations occupy a position internal to the wolffian ducts, or ducts of the mesonephros. All this takes place in embryos of about 10 millimeters. The later development and importance of these tubes differs in the different sexes. In males all of the tubes disappear except the extreme ends, the upper becoming the unimportant little cystic structure known as the appendix testis, and the lower the prostatic utricle, the vagina or uterus masculinus.

In the female, on the other hand, the whole length remains to form structures of great importance. The upper trumpet shaped expansion becomes the fimbriated extremity of the fallopian tube, the central parts become the oviducts, and the lower parts having received an investiture of mesenchyme, become fused at about the fourth month to form the vagina below and the uterus above.

If one recall the primitive and purely cellular character of the early embryonal tissues forming these structures, and picture the various consequences that might result from the ameboid wandering of some of the superficial cells; the dislocation of cells or groups of cells in the elongations, fusions, insertions, multiplications, and close approximations of the various groups of cells; of their growing importance at one time and waning importance at another; the admixtures and reinforcements that some of the cell groups receive from the myotomes, and the close relation to the subjacent sclerotomes and myotomes, it may appear to be more remarkable that the process of development takes place in so regular and orderly a manner than that it should occasionally meet with accidents resulting in dysontogenesis.

Dysontogenesis is the term used by Schwalbe to express accidents of development that may be followed by malformation or tumor occurrence. With the malformations we have, at present, nothing to do; our interest centers about the tumors, and the means of accounting for them.

The importance of dysontogenesis as a means of explaining the complex tumors was fully realized by Wilms, and brought out clearly in his writing upon "Die Mischgeschwuelste." It is certainly the most satisfactory theory by which to explain the origin of tumors characterized by the presence of heterologous tissues—"mixed tumors"—though some pathologists still prefer the old theory of metaplasia. Metaplasias probably do occur, but the theory has been much overworked.

Dysontogenetic tumors have no standards of histological structure. Some, like the two botryoid vaginal tumors of which mention was made previously, appear as simple tissue tumors, and may be such; others are compounded of several tissues and are correspondingly complex. Perhaps all are really "mixed tumors," but failure to detect any tissue mixture makes it better to speak of them as ontogenetic or dysontogenetic.

It certainly seems paradoxical to speak of "mixed tumors" that are not mixed in so far as their histological structure is concerned. But how "mixed" must a tumor be to be classified as such? Among the tumors of the four organs here considered, the bladder, the prostate, the uterus, and the vagina, there seem to be all gradations between those composed of tissue of one kind only, and others with a highly complex combination of tissues. In all of these organs there are many reported cases of "mucous polyps," "edematous fibromata," "myxomata," "myxosarcomata," and "sarcomata," in which the structure seems to be so simple that no one seeing one for the first time, would ordinarily think of regarding it as otherwise. The first of the cases that came under my own observation seemed to be of a very simple structure, and in consequence, was called "sarcoma." I did not realize until after I had studied my second case, how few, unobtrusive, and uncertain the rhabdomyoblasts, whose presence would change the diagnosis to mixed tumor, might be. In the cases reported in the literature one finds that the discovery of a very few striated muscle cells invariably leads to the diagnosis rhabdomyoma, a recognized type of mixed tumor.

The discovery of a single muscle cell is sufficient to make the tumor a rhabdomyoma. But if the muscle cells are very few and far between, they may not be found. It may, therefore, not be possible to identify all mixed

tumors as such. Dysontogenetic is therefore a better term to employ.

Perhaps the matter can be better understood by reference to the other extreme of the series. The most complexly mixed tumors are found in the bladder and uterus, and contain bone, cartilage, muscle, nerve fibers and cells, adipose tissue, occasional chromatophores, and of course numbers of blood and lymph vessels in variable proportions. Attempts to provide such tumors with appropriate descriptive names have resulted in the elaborate and meaningless terminology mentioned.

Where the diversity of the tissue is so great, there is usually little question about the tumor being called a "mixed tumor," even though the author may prefer to account for the diverse tissues through metaplasia.

Cartilage is one of the most variable of the tissues found. In many of the uterine and vesical tumors it is absent; in others the quantity is small, in still others there is so much, and so little else, that the tumors have been described as chondromata, chondrosarcomata, osteosarcomata, etc.

It has been suggested that the age of the patient in whom the tumor occurs has something to do with the differing tissue components and their proportions. In general, the older the patient, the greater the variety and the better the differentiation of the component tissues. The 74 reported cases of the very soft and simple botryoid tumors of the vagina all occurred before the twenty-second year, and the only heterologous elements found in them were striated and unstriated muscle cells, some nerve bundles, and occasional unaccountable epithelial cells. Of 164 vaginal tumors, a single one, Mann's case, 31 years old, contained cartilage.

Of the 77 vesical tumors collected, 61 occurred before the twenty-second year, and nearly all were very soft and simple, much like the vaginal tumors. Of 48 prostatic tumors, 38 occurred before the twenty-second year, and most of them were very soft in consistence and simple in structure.

But age alone does not adequately explain the structure for soft botryoid tumors of the uterus rarely occur until much later in life. Of 274 uterine tumors, 34 of which occurred before the twenty-second year of life, only 22 were soft botryoid tumors, while 39 similar tumors occurred after that age, the oldest patient being 69 years of age.

The presence of heterologous tissue elements constitutes the characteristic feature of the mixed tumor, and their presence is most satisfactorily explained by assumed early accidental dislocations of embryonal cells and their inclusion among others retaining their normal positions.

The cells thus dislocated may be conceived to meet with any one of the following fates: (1) the dislocated embryonal cell or cells may be suppressed and extinguished by the more vigorous growth and development of the normally situated cells; (2) they may continue to live and complete their own differentiation in the abnormal environment at the same time as the normally situated cells, with the occasional occurrence of such congenital anomalies as the presence of striated muscle fibers in the myometrium, etc; (3) they may remain latent, alive, and potentially vegetative for any length of time, and at any moment initiate the growth of a tumor.

Some imagine that the dislocation supposedly taking place at a very early period of embryonal development, when both the normally placed and the dislocated cells are equally potent, must inevitably show itself through immediate malformation or tumor development. It may, but rarely does so. In the cases reported by Nehrkorn and Girode, in each of which striated muscle fibers were found in the myometrium of an otherwise normal uterus, it may be assumed that both normally and abnormally placed cells developed simultaneously. In those cases reported by Martin, Williams, and Bowers in which the child was born with a vaginal tumor already in existence and projecting from the vulva, the two may have developed simultaneously, the misplaced tissue excessively. Five of the reported vaginal tumors made their appearance within a few months and 10 others within a year after birth. But it is not necessary for them to appear so early, for 10 supposedly similar uterine tumors did not appear until after the fiftieth year of life. Presumably embryonal cells can and often do remain latent and

potential for many years, as is evident in the case of "uterine fibroids," about which more will be said later.

Dysontogenetic tumors may not all be the result of embryonal dislocation. Some are homologous, and consist of, or are derived from, tissue elements normal to the part in which they occur. To explain them is one of the great problems of oncology, and, as yet, no explanation has been found generally satisfactory.

Cohnheim, who seems to have given the most rational theory, has been much misunderstood and much misquoted. He supposed that in the embryonal formation of each of the tissues, more cells are furnished than are actually needed, so that among those that develop and differentiate some are left over as though to serve for future emergencies—regeneration, etc.; as they retain the potentialities of future development into normal tissue, so also, they possess the potentiality of tumor development.

If the edematous fibromata, mucous polyps, myxomata, etc. with which the tumor series begins, be as simple as they appear, they may have their beginnings in residual embryonal cells normal to the part, but not used up in its development. If dislocated heterologous embryonal cells accidentally included in any part explain the occurrence of a complex tumor, there is no reason why homologous embryonal cells belonging to it should not explain the occurrence of a simple tumor. The only remaining question would seem to be the possible presence of such superfluous cells anywhere. Perhaps this matter may be cleared by a brief consideration of the "uterine fibroids."

Uterine fibroids—leiomyomata or leiofibromyomata—are very common tumors, whose origin was for a long time assumed to result from the active vegetation of some of the cells of an originally normal myometrium. If the tumor was single, it was even imagined that it might result from an abnormally acquired vegetative activity of a single muscle cell; when, as was frequently the case, the tumors were multiple, of scattered cells. No explanation of the remarkable fact that only occasional muscle cells thus misbehaved was ever given, nor was it remarked that all of the cells never became simultaneously vegetative with hypertrophy of the entire myometrium and a resulting gigantic uterus. Von Recklinghausen pointed out that the development of the tumors might be referred to defects in the fusion of the muellerian ducts to form the uterus, some of the myoblasts designed to form the myometrium then becoming accidentally displaced and remaining sequestered until, at some future time, they began to multiply, eventuating in nodes of muscular tissue enclosed in, but not a part of, the uterine body, and so became tumors.

If true, this proves that embryonal muscle cells, at least, can be sequestered, and may remain latent in the surrounding adult tissues until, many years later, the growth of a tumor reveals their unsuspected presence. Such tumors are dysontogenetic and homologous.

But many fibroids, though apparently simple in histological structure, behave unexpectedly, and may manifest clinical malignancy, through rapid growth and metastasis. In such cases it is usually only one of several fibroids that shows this change, and not infrequently it is only some of the cells of the fibroid that assume the excessive vegetative growth, so that the behavior of those ceils is, with respect to the tumor, exactly like that of the sequestered embryonal cells in the uterus was with respect to the myometrium. Curiously enough this abnormality of the tumor has received exactly the same explanation that was originally accorded to the occurrence of the fibroids themselves. It is supposed to depend upon an acquired change in vegetative activity on the part of one or a few of the *tumor* cells. But may it not rather depend upon the presence of still other remaining embryonal cells?

It was early discovered that fibroid tumors were occasionally complicated by the presence of endometrial tissue with its characteristic epithelial tubules, and such tumors were called "adenomyomata."

The endometrial elements were difficult to account for, and elaborate theories were propounded, as, for example, that as it grew, the fibroid dislocated, and dragged some of the subjacent endometrium into its own sub-

stance, where it grew *pari passu* with the tumor. How much easier it seems to account for the presence of the endometrial tissue on the ground of dysontogenesis, and remembering that the muellerian ducts not only furnish the material for the formation of the myometrium, but also for the endometrium, assume that in the defective amalgamation of the tubes, both embryonal myometrial and embryonal endometrial tissue elements were dislocated and sequestered, the subsequent complexity of the tumor resulting from the later and simultaneous development of both. But this is again a homologous tumor and though it may very well be dysontogenetic cannot in its usual meaning be called a "mixed tumor."

It is interesting because unusual to observe the presence of heterotopic tissues, both in the uterus, and in tumors of the uterus. In my collection of microscopic slides there is a section of what at first appeared to be a perfectly formed and normal uterus, upon one side of the body of which there was a pale spot about 1 centimeter in diameter. Upon examination it proved to be a mass of adipose tissue. There is no reason to regard it as a tumor, there was no enlargement; it seems simply to be a malformation that resulted from the dislocation and inclusion of some neighboring lipoblasts among the myoblasts out of which the uterus was developed. It did, however, cause a defect in the continuity of the myometrium, and in case of pregnancy might have predisposed to rupture of the organ.

The presence of adipose tissue in the uterus has frequently been observed and takes numerous forms. Lebert has reported a case of adipose tissue in the wall of the uterus; Williamson and Brockman, and T. Smith have all referred to Specimen No. 3001 in the museum of St. Bartholomew's Hospital, in which there is an encapsulated lipoma in the wall of the uterus near the fundus; Sitzenfrey reported a case in which adipose tissue ramified among the muscular bundles of a leiomyoma of the uterus. Glass found adipose tissue in 11 out of 938 leiomyomas; Stroinski observed a small lipoma of the anterior lip of the cervix that hung down as a covering of the os, so as to cause sterility until removed.

In a paper published in 1906, A. G. Ellis placed the number of reported cases of true lipomata of the uterus at 11.

The appearance of heterotopic adipose tissue in the uterus, sometimes in the form of an indefinitely circumscribed mass in the myometrial substance, sometimes in the form of a circumscribed and encapsulated tumor, and sometimes ramifying in all directions among the muscular bundles of a fibroid, certainly seems to be the result of a developmental disturbance rather than of a "metaplasia."

The same is true of other heterotopic tissues. R. Meyer found a mass of cartilage in the cervix of an otherwise normal fetal uterus; Gallerani reported the discovery of a "cartilaginous nodule in the body of the uterus"; in 3 of Hartfall's cases of "mixed tumors" cartilaginous nodules were found in endometrial scrapings.

The occurrence of heterotopic bone is rare. It is occasionally found in vesical tumors, in uterine fibroids, and in the complicated mixed tumors of the uterus occurring in later life. In 2 cases, those of Benecke and Shattock, it has been reported as occurring in bladder tumors. Benecke's patient was a man 71 years of age, in whose bladder there was a mass the size of a small apple, the center of which was bone with well defined Haversian systems, surrounded by a mass of fibrochondroid tissue. Other tumors containing bone have been reported by Meyer, Pernici, Pfannenstiel, and Wolf.

Nervous tissue is the rarest of the heterotopic tissues to be found in the region under consideration. Amann in an infantile vaginal tumor, found striated muscle, solid strands and gland-like alveoli of epithelial cells, bundles of thick nerves and ganglionic nerve cells. The most remarkable tumor of this kind was reported by Kleine, whose adult patient had a medium sized degenerated fibroid of the fundus of the uterus and entirely separate from it, in the lower part of the uterus, projecting externally, and forming a rounded mass almost the size of an egg, an independent tumor mass, of paler color, made up entirely of well formed and fully medullated nerve fibers. From the standpoint of the present

discussion this appears to be of immense importance, for not only is the tissue heterologous, but also adult, and of a very peculiar kind, impossible to account for through metaplasia. How could a tumor mass of nerve fibers thus occur? The most simple explanation seems to be the assumption that at a very early stage of embryonal development, there had been dislocation of neuroblasts, that had multiplied excessively, differentiated, giving off fibrils as they matured so far as medullation was concerned. The nerve fibers thus formed, having nowhere to go, and nothing to do, had persisted while the cells by which they were formed had degenerated and disappeared. In large retroperitoneal ganglioneuromata it is not uncommon to see the sympathicoblasts multiplying freely, partly differentiating into ganglion cells, and these undergoing vacuolar degeneration and disappearing, leaving their fibrils and surrounding Schwann cells to form the bulk of the stroma of the tumor.

A number of the tumors found in the region under consideration have been described as melanotic (melanotic sarcomata). The cases reported by Boldt, Graefe, Matthews, Smith and Luch, and Stefani, all occurred in adults. It was at first conceived to be impossible that these tumors had anything whatever to do with the principles of dysontogenesis or embryonal dislocation. There seemed to be no reason for assuming that melanoblasts either belonged in the parts or were in the neighborhood. But since it has been shown that melanoblasts may be but satellite cells of the nervous system, and as nervous tissues are occasional components of dysontogenetic tumors, it becomes quite possible.

It may occur to the reader that if the theory of dysontogenesis with the dislocation of embryonal cells be granted, definite distribution of the dislocations must result from the anatomical relations of the embryonal parts. That is correct and it was pointed out at the beginning of this paper, that there is a fairly regular distribution. The tumors are most frequent in the uterus, then in the vagina, then in the bladder, and lastly in the prostate. They occur very rarely in closely adjacent regions. Guersant's botryoid tumor is said to have occurred in the vulva; Lannois's tumor in the prepuce of the clitoris; Serafini's tumor seemed to arise from the urethra, and Rokitansky's tumor, occurring in a lad of 18 years, was near the anus. More of the uterine tumors were of the corpus than of the cervix; more of the vaginal tumors arose from the anterior wall than from the posterior wall, while a very few were scattered over the vaginal wall as though multicentric. Vesical tumors were much more frequent in the region of the trigone than elsewhere. The few and slight departures from these positions may be attributed to the growth movements of the embryonal structures, and to the ameboid movements of the dislocated cells, that may be imagined to be striving vainly to regain their normal relationships.

The histological variation of the tumors, and the differing proportions of their tissues result from the kind of cells dislocated, the number of cells dislocated, and the ease or difficulty with which their evolution is effected in the abnormal environment in which they find themselves.

No one has the slightest information as to the forces that initiate or determine tumor growth. In some cases it seems to be related to hormonal activities, as in the case of uterine fibroids; in others to general or local metabolic variations. It is hard to refer ontogenetic tumors to "irritation." But, however it begins, once the neoplastic growth is under way, variations in the results may be expected in consequence of the number, kind, and position of the cells forming the primordium of the tumor, and their possible interference with one another.

Should the tumors arise from homologous residual embryonal cells of one kind, there will be only one type of tissue, and the tumor will be simple; if from several kinds of cells, the tissue resulting from the most successful cells will preponderate. Where there are several types of cells and resulting tissues, that possessed of greatest vegetative activity will preponderate unless it meets with some kind of mechanical or chemical interference. It can, at least, be imagined that that tissue which gets and keeps the best start will preponderate over all others, and its predominance may not

only be quantitative but qualitative. The dominant elements, through multiplication or differentiation or both, may so interfere with others as to suppress their evolution and maintain them in the embryonal cellular state.

For this reason an overwhelming number of the tumors contain larger or smaller numbers of undeveloped and unidentifiable cellular elements that lead to the tumors being classified among the sarcomata. The term "sarcoma" appears so constantly in the nomenclature of these tumors as to give the impression that there is full justification for it. Indeed, the clinical behavior of the tumors seems to support this view, for almost without exception they are malignant, recur again and again, and eventually destroy life.

REFLECTIONS UPON THE NATURE OF SARCOMA

At first glance it may seem as though the discussion of this question is widely removed from the scope of this paper, but it is unavoidable, for without it much of importance will have to remain in the dark.

Etymologically the Greek word "sarcoma" means simply "fleshy swelling" or "lump of flesh." The word is in such every day use among clinicians, pathologists, and histopathologists as to suggest that it is well understood. As a matter of fact, it is so vague as to have very little real significance. By various authors different definitions are given, but nearly all agree upon the following general principles: (1) sarcoma is a malignant tumor; (2) it occurs chiefly in the young; (3) it consists essentially of cells; (4) the cells are of mesoblastic origin; (5) the cells are of embryonal type; (6) they represent the early form of the connective tissues.

Three different conceptions enter into the wording of most definitions: malignancy, which is clinical; cellular structure, which is histological; and mesoblastic derivation, which is embryological. Not one of these is constant.

1. *Malignancy.* It is extremely variable, and runs the whole gamut from tumors that are quickly and widely metastatic and fatal, through those that grow slowly, and recur again and again after removal, to those that seem to be cured by a single excision. Tumors as variable as this cannot all be the same.

2. *Cellular structure.* The cellular variations are remarkable. There are small round cell tumors, oat-shaped cell tumors, small spindle cell tumors, large spindle cell tumors, mixed cell tumors, in which there are both round and spindle cells, large round cell tumors, irregular cell tumors, and pigmented cell tumors. All of these were said to be sarcomata, until it was discovered that a good many of them belonged in other categories. But why were they at first, and for so many years regarded as sarcomata? Simply because they were cellular tumors, the cells of which could not be identified. The first subtraction from the group probably began with Marchand who found little globes of cells, having a central tuft of delicate fibrils, in a small round cell sarcoma of the adrenal region, and pointed out that the cells thus arranged and characterized were undoubtedly "neuroblasts," and slightly more advanced in evolution than the generality of the cells that were "neurocytes." Many other tumors of the same kind have since been found, but they are no longer spoken of as sarcomata; through ability to identify their cells they have now become neurocytomata and neuroblastomata, and with the more correct understanding of the cells, it became necessary to modify the embryological conception of the tumor. The blastodermic derivation of nervous cells is ectodermal, not mesodermal; the cells are not embryonal connective tissue, they are nerve cells. That the tumors are clinically highly malignant makes no difference, they have ceased to be sarcomata, and have become malignant neuromata.

Large tumors of the anterior mediastinum, composed of small round cells were some years ago called "small round cell sarcomata," then with improved cytological technique were more specifically called "lymphosarcomata." But recently ideas changed with respect to the embryonal derivation of the thymus, and its small cells began to be regarded by an increasing number of embryologists and histologists as epithelial and ectodermal in origin, when, of course, it at once became necessary to change the name of the tumors, which are now generally known as "thymomata," and regarded as belonging in the carcinoma class.

Certain "small cell" tumors of the lung and of the prostate were for years unhesitatingly regarded as sarcomata, but with more careful study have been recently reclassified as small cell carcinomata. It seems, therefore, that it is chiefly when the real type and derivation of its cells are not known that a tumor is a sarcoma. So soon as they can be correctly identified, the tumor is removed from the rapidly shrinking sarcoma class. This is not only true of tumors composed of small round cells; it also applies to those composed of spindle cells. Tumors occurring along the course of nerves, and composed of long spindle cells were formerly called sarcomata. The cells were thought to be connective tissue cells, and of mesodermal origin, but with modern methods of study, are now believed to be derived from the cells of Schwann, and of ectodermal derivation. Such tumors are now called Schwannomata, and, of course, are removed from the sarcoma group. Other examples might be given did space permit.

3. *The mesoblastic derivation of the cells.* It is easy to declare upon academic grounds alone that each tissue can be referred to one or other blastodermic layer, and therefore, any tumor having a structure seemingly identical with it, must be derived from the same blastodermic layer, but in practice it becomes almost impossible.

Evidences of this difficulty have already been cited in the case of the neurocytoma, the thymoma, the Schwannoma, and the carcinomata of the lung and prostate. But it obtains in many other cases. Many tumors, today unhesitatingly described as carcinomata, were, in the past described as "aleveolar" sarcomata, and supposed to be of mesoblastic derivation, upon the purely theoretical ground that there could be no ectodermal derivations in those parts of the body in which the tumors occurred. We now recognize the occasional heterotopic presence of abnormal tissue elements of unexpected blastodermic derivation almost anywhere.

Tumors of the urogenital apparatus perplex us because all of the epithelial elements are supposedly mesoblastic. Shall carcinomata of the uterus be called sarcomata because of the blastodermic derivation? Many tumors of the ovaries and testes, being almost purely cellular are impossible to classify because the cells lack sufficient characters by which to classify them.

From the time of Virchow until quite recently, all of the tumors of the melanoma group were known as "melanotic sarcoma" because the tumors were purely cellular, malignant, and composed of cells, which though pigmented were so indefinite as to be regarded as mesodermal in origin and of connective tissue type. Only recently, and largely through the work of Masson, it has come to be generally considered that melanoblasts are cells of ectodermal derivation, belonging in the category of satellite cells of the nervous system, and that the pigmented tumors are therefore not sarcomata at all.

But there are many to whom Cohnheim's theory of residual embryonal cellular material does not appeal and who look for some other means by which to account for the embryonal or embryonal appearing cells in the tissues of tumors. A theory popular at present is that of Hansemann and is described as *anaplasia*. It teaches that through rapid multiplication of cells their specialization and essential characterization are gradually lost, so that with each generation of multiplying cells there is a more and more complete return to the embryonal appearance and behavior. Whether or not such a change is possible is uncertain. It could apply only in cases in which the cell differentiation did not preclude multiplication as it often does. Under every kind of adverse condition highly specialized cells die and disappear. Evidence in support of the theory of anaplasia is supposed to be manifested by certain uterine fibroids that grow rapidly and finally show themselves to be clinically malignant (metastatic).

Fibroids when examined present interesting variations in structure. Some are purely muscular—there is naturally always some interspersed fibrillar tissue surrounding and supporting the blood vessels just as is the myometrium—and appear to be finished and inactive neoplastic formations, while in others one or several foci may be found in which the cells are vegetating, and show such modifications as are incidental to multiplication—larger

size, metachromatic nuclei, karyomitotic nuclei, etc. In a few cases the whole tumor may seem to be thus engaged in rapid growth and from some such tumors occasional cells may be distributed by way of the blood stream, with resulting distant metastases. Such malignant metastatic tumors are usually called leiomyosarcomata, though there is no valid reason for the use of the term "sarcomata," the cells are muscle cells and the tumors are in reality *malignant myomata*.

In another group, among the muscle cell bundles, either widely distributed, or locally collected, strands or groups of small spindle cells may be found. These are totally unlike muscle cells, and in no manner traceable to them. Their rapid multiplication results in an entirely new type of neoplastic tissue, exactly like spindle cell sarcoma as seen elsewhere, and in metastases bearing no resemblance whatever to muscular tissue. These tumors are always called spindle cell sarcomata, and with greater justification. Here, therefore, are two entirely different conditions, called by the same name, one of undoubted myogenic origin, the other apparently not. Unfortunately, this has given rise to the supposition that the muscle tissue, through anaplasia, has changed into connective tissue, and so undergone a "sarcomatous change." In the first instance there was no change; the tumor originally consisted of muscle, and although its cells rapidly multiplied, they remained muscular cells. In the second instance, however, the tissue through the dissemination of which the metastasis took place, was of an entirely different kind, that only by stretch of the imagination can be regarded as having originated by anaplasia from the muscle cells. It would be strange if rapid multiplication of the cells should result in anaplasia in one case and not in another!

It is not unusual to find among multiple fibroid tumors some that present the usual muscular structure, and some made up partly of muscle and partly of small spindle cells like those described as characteristic of spindle cell sarcoma. If we are willing to admit the probability of the adenomyomata being dysontogenetic, and the result of embryonal endometrial inclusion, it is difficult to escape the conviction that the other varieties may originate in the same manner. There are also occasional malignant and metastatic fibroids in which the two types of cells grow together, both appearing in the metastases. These are often adduced to prove that the one type of tissue has transformed or is transforming itself into the other, and transition steps are sometimes pointed out, but nothing is more hazardous than an attempt to derive one tissue from another by pointing out the intermediate steps. It is more probable that the transformation is imaginary and that the different tissues have existed side by side as the result of dysontogenesis.

But what is the true nature of the cellular tissue the presence of which characterizes sarcoma? It seems probable that it is residual, embryonal cellular tissue sequestered or dislocated. What kind of tissue antecedent it is may never be discovered because it has not evolved; it is simply *undifferentiated cellular substance*.

It is because of the presence of more or less of such undifferentiated cellular substance that the great majority of the mixed tumors have been called either sarcoma or some variety of sarcoma.

This brings up the last question, what is sarcoma? Is it not possible that it is nothing but vegetating, proliferating, undifferentiated, residual embryonal cellular substance sequestered, either in its normal environment or dislocated from it, until traumatism, metabolic or hormonal stimulation, or some other cause determines that it shall result in a tumor?

Looking over the literature, one finds that inability to identify the character of the cells in a tumor has sometimes resulted in the grossest errors of diagnosis and frequent abuse of the term "sarcoma."

In 1894 a tumor with a remarkable variety of cells large and small, single and syncytial such as I had never seen, came under my own observation. In the absence of any familiar appearances and "by exclusion" it was described and reported as a "large round cell sarcoma of the uterus." Years afterward, "syncytioma malignum" began to receive attention as a new variety of tumor, and

remembering the peculiarities of that just mentioned, I reviewed the slides, and found out what it was. The confusion becomes even worse if the cells seem to the pathologists to resemble those of some unusual though recognized type. In this way many tumors have been described as "endotheliomata" that upon renewed study resolve themselves into entirely different types of tumor. A review of the illustrations in some of these publications may be sufficient to show that commonplace carcinomata have sometimes been described under this doubtful and ambiguous term "endothelioma."

Not long ago two tumors were brought to me as "sarcomata" of the vagina. They were of entirely different histological appearance though each was essentially made up of spindle cells. One had occurred upon the anterior vaginal wall and had promptly recurred after operation, while the other, located upon the posterior vaginal wall showed no return. Careful histological study of these two tumors showed each to be made up of easily identified elements. The former consisted of small spindle cells, so arranged that the whole structure seemed to be made up of little rosettes, in the centers of which were occasional tangles of very delicate threads, almost unmistakable evidence of the nervous origin of the tumor, which was in all probability a malignant neuroma. The other tumor was composed of larger, longer, and more slender parallel spindles that usually assumed a wavy course with frequent palisades of nuclei, and other appearances familiar to all who have had experience with the Schwannomata. The final identification of these tumors came as a surprise to the first observers, but had they known or remembered that tumors of the vagina, bladder, and uterus containing ganglionic nerve cells, medullated and unmedullated nerve fibers, had been recorded, the surprise would have been less.

DIAGNOSIS

The histopathological diagnosis of the dysontogenetic tumors is easy or otherwise according to their structure. When the tumor consists of a variety of tissues, some distinctly heterologous (mixed tumors), there may be no trouble, but when its structure is simple, it becomes more and more difficult to be sure of its nature, and in some cases may be purely a matter of opinion. This is particularly the case with the vaginal, vesical, and prostatic tumors of infancy and early life, described in the literature as edematous fibromata, myxomata, or sarcomata, and with the uterine fibroids. In spite of what has been said, some pathologists will no doubt prefer to regard the simple appearing tumors as simple "blastomata" and "sarcomata," but it is hoped that the significance of their relative positions as extremes in a long series of tumors of increasing complexity will not be disregarded.

PROGNOSIS

All dysontogenetic tumors must be regarded as potentially malignant. The malignancy shows itself in different ways in different tumors, and at different ages. The botryoid tumors of early childhood show it through repeated recurrence, and local invasion followed by obstructions, ulcerations, necroses, infections, and hemorrhages. Metastases are rare: Dugge saw a pleural, and Sutton a pulmonary metastasis from vaginal tumors of little children; the case herein reported had local metastases upon the peritoneal surface of the broad ligaments, ovaries, and the fundus of the uterus.

The tumors of adults are somewhat more apt to be metastatic: Delagienière and Beauchef saw a tibioperoneal metastasis from a uterine tumor containing bone and cartilage in a woman 54 years of age; Hartfall saw two adult intra-uterine tumors containing cartilage cause death through metastasis to the lungs; Heddaus saw a metastasis to the pleura from a botryoid tumor of the uterus in a woman aged 48 years; Graefe saw a patient 22 years old with melanotic sarcoma of the vagina die with metastasis to the lungs; one of Kaschewarowa-Rednewa's cases of botryoid tumor had a metastatic nodule in one kidney; Smith saw metastatic nodules in the great omentum; Stefani reported a case of melanotic sarcoma of the vagina in a woman 68 years old, who died with metastasis to the liver; Graefe also saw a woman aged 22 years, with a melanoma of the vagina, die of pulmonary

metastasis and Rein saw metastatic nodules in the pelvic lymph nodes and wall of the vagina in a woman 21 years of age with "sarcoma enchondromatodes arborescens colli uteri." But, all told, excepting those cases described as "sarcomatous degeneration of uterine fibroids," there seem to be only about a dozen cases of metastasis, near and remote, recorded in the literature.

TREATMENT

When the usual course of the tumor is, as in the case of the botryoid type, repeated recurrence, local invasion of the surrounding tissues, and death from obstruction of the urinary passages, little can be expected from operative treatment, and in almost all cases it fails, and the patient dies. In very rare cases, and when, as sometimes happens, a vaginal tumor is situated upon the posterior wall, operative removal may succeed. The recovery that followed a second operative removal in one of Frick's cases (Schuchardt's case) is attributed to that tumor having been so situated. This patient was living and well 10 years later. Edibohls has reported a case of adult vaginal sarcoma that remained well for 3 years and 3 months after operation, but in almost all of the reported cases the patients have died.

Treatment by X-rays and radium seemed to offer a better means of attack, but experiences with them have not been followed by the happy outcome that was hoped for. The patient reported by Halle, Grisel and Veau, who was 2 years of age when the treatment for a botryoid vaginal tumor was begun, is said to have been kept alive for 7 years through repeated radium treatments, though she finally died of the tumor. Adler, Doederlein, and Reisach have each reported a case "cured" through courses of radium treatments, but through private correspondence I learned from Adler that his patient finally died of sepsis—one of the natural terminations of the tumor. Doederlein kindly wrote me that his little patient was alive and free from recurrence a year after the treatment was begun, but the period is, of course, entirely too short to make sure what the final outcome may be. Reisach probably failed to receive my letter as he did not answer it. The present condition of his patient is, therefore, not known, though again, the time that elapsed between the treatment and its reported success is not sufficient to convince one of the future safety of the patient.

A considerable number of recoveries after operation for the removal of "malignant leiomyomata" are on record, but inasmuch as there are no satisfactory microscopical criteria for determining the malignancy or benignancy of such tumors, and as many of the reported cases had never been microscopically examined, it is impossible to tell what the tumors really were.

CONCLUSIONS

A considerable and miscellaneous variety of tumors that develop from, or in close proximity to those embryonal structures that enter into the formation of the urogenital sinus, are most easy to account for upon the basis of origin through dysontogenesis.

The most characteristic of these tumors, being composed of several different and easily identified tissues, some of which are foreign to the part—heterologous—are readily assigned to the class known as "mixed tumors."

Others of simple structure and therefore not appearing to be mixed tumors, through their localizations, clinical appearances, and behavior seem also to belong in the dysontogenetic group.

The frequent occurrence of the tumors at a very early age, and the distinctly embryonal nature of their tissues suggest origin from residual embryonal cellular material such as Cohnheim first pointed out. Almost all of the tumors contain larger or smaller numbers of undifferentiated embryonal cells, of which the true nature is obscure.

When a large number of the tumors is arranged in series, the structure is found to pass by gradations to greater and greater histological complexity, and the appearance of heterologous tissues. It seems reasonable, therefore, to assume that the complexity and heterologousness depend upon the dislocation and inclusion of cells or groups of cells of the primitive embryonal substance, and their subsequent development in the heterotopic posi-

tion. Thus dysontogenesis may account for all of the various tumors discussed.

The tumors are all potentially malignant, and most of them actively so.

It is believed to be an error to think of these tumors as varieties of sarcoma and their relation to sarcoma and the probable nature of sarcoma are discussed.

The literature of the subject is so confused through complicated terminology, incorrect identification of individual tumors, premature publication of cases declared to be cured after operation or other treatment, the designation of certain tumors—uterine fibroids—as malignant, from histopathological appearances the exact significance of which is not understood and may be in no manner indicative of malignancy, that a careful analysis of it has resulted in little of value.

Except in the case of the tumors in the group of "uterine fibroids," very little seems possible in the way of successful treatment. Surgical operations, irradiation by X-rays and radium, alike usually fail to prevent recurrence or to save life.

Note.—The original manuscript of this paper was accompanied by numerous tabulations, lists, and classifications, and followed by a bibliography comprising 513 titles and references. As they may be valuable for reference to some of the readers of the paper, and as it required several years to collect and arrange them, copies will be placed with the American College of Surgeons and the College of Physicians of Philadelphia where they may be consulted.

CLINICAL SURGERY

FROM THE GLASGOW MEMORIAL HOSPITAL

TRANSPLEURAL NEPHROPEXY

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IN 1913 Mr. Maylard published his classical work *Practice and Problems in Abdominal Surgery*. In that book he briefly but masterfully described in Chapter XXII his operation for the fixation of the abnormally mobile kidney. He had employed that method for some years prior to publication; that account of the operation may, therefore, be taken as the result of his mature experience.

Having had the privilege of being his assistant for some years, I have had the advantage of acquiring direct from the author the details of the operation as performed by him. Possessing now at this date a comparatively large personal experience, and having introduced several modifications of the original technique, the time appears opportune for the presentation of a further communication on that subject. Following upon a few preliminary anatomical, physiological, and etiological remarks, I will endeavor to describe the operation as it is performed at this date.

ANATOMY

The structures directly involved in the performance of this operation are the pleura, the diaphragm, the structures occupying the intercostal space, the kidney, and the posterolateral abdominal wall. The lung will be described because it might be involved but it should not be. I will endeavor to describe the parts with relative accuracy in the order in which they are encountered during the performance of the actual operation.

Posterolateral abdominal wall. The incision is made transversely half an inch below the level of the tip of the twelfth rib, skin, subcutaneous tissue, superficial and deep fascia, posterior layer of the lumbar aponeurosis external oblique, internal oblique and transversalis muscles are divided in order named, when the pararenal and perineal fat are reached and cleared aside.

The triangle of Petit. Base is formed by the middle third of the iliac crest, its apex by the overlapping of the external oblique and latissimus dorsi, its anterior boundary by the posterior border of the external oblique, and its posterior boundary by the anterior border of the latissimus dorsi. The roof is formed by skin and fascia and its floor by the internal oblique.

Kidney. The organ by means of which many of the waste products of the body are eliminated. The kidneys are situated postperitoneally, embedded in fatty areolar tissues mainly in the hypochondriac and epigastric regions, but they also extend to a variable extent into the lumbar and umbilical regions. It may be said that a considerable diversity of opinion exists as to their exact position and its normal variations.

In the adult the kidneys weigh 5¼ ounces, and they are said in the adult to account for one two hundred and fortieth of the total weight of the body. In the infant they form one one hundred and twentieth of the total body weight. Their weight is said to be slightly less in the female. They are bean shaped and of a dark reddish brown color, slightly mellowed by their grayish white, glistening capsule. Their component parts are: two borders, two surfaces, and two extremities.

Their posterior surface rests upon the perirenal fatty areolar tissue, which rests upon the fascia covering the diaphragm, quadratus lumborum, and psoas muscles, the eleventh and twelfth ribs, and the transverse process of the first and second lumbar vertebræ and sometimes that of the third; the twelfth dorsal, ilio-inguinal and iliohypogastric nerves along with the anterior divisions of the first and second lumbar arteries and veins.

The external renal border is convex in its upper two thirds and in the right kidney is in contact with the liver, in its lower third with the colon, and rests upon the aponeurosis of the transversalis abdominis. The left is in contact with the pleura.

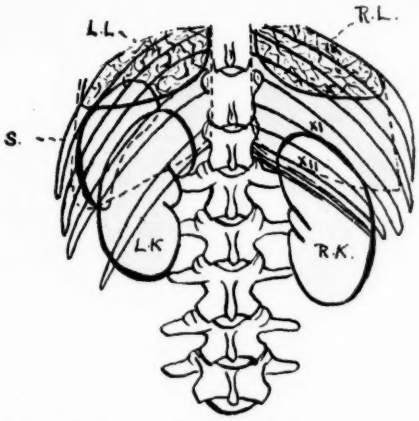

Fig. 1. Diagram showing the posterior relations of the kidney.

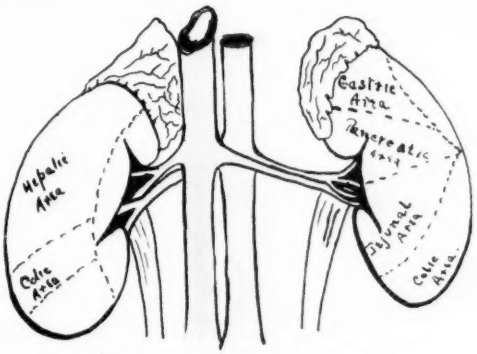

Fig. 2. The anterovisceral relationship of kidney.

The internal renal border is concave, and in the case of the right kidney, is in close proximity to the inferior vena cava; that of the left kidney is 1 inch from the abdominal aorta. This border presents the hilum which is situated approximately in its middle third and has an anterior and posterior lip within which is the sinus occupied by the renal vessels and veins in the following order from before backwards: veins, arteries, ureter, nerves, and lymphatics. From above downward: right kidney, vein, artery, ureter; left kidney, artery, vein, ureter.

The arterial supply (Fig. 2) is derived from the aorta, via the renal, suprarenal, spermatic or ovarian and lumbar. The right renal vein empties directly into the inferior vena cava, while the left, which crosses over the abdominal aorta, as a rule receives the ovarian or spermatic, according to sex, and in certain cases the inferior phrenic and suprarenal.

The nerve supply is mixed. Fibers of spinal origin are derived via the small and least splanchnic and vagus through the celiac plexus. The sympathetic supply is derived from the aortic nerve ganglion and celiac plexus.

The lymphatics are disposed in two sets, superficial and deep, and drain into the lumbar glands.

The kidneys may vary in form, size, position, and number. Any variety from the normal may be encountered. They may retain the lobulated form of infancy or they may be round and triangular as in the form of a horseshoe, thus forming only one kidney. One kidney may be very much reduced in volume; if so, as a rule the opposite is much larger. Variations in number are comparatively infrequent, the horseshoe variety, being perhaps the most common, but one kidney may be entirely absent, or there may even be three! If a third is present then it is usually situated in a mesial position.

The kidneys are situated in the renal fossæ and maintained in that position by their relations with adjacent structures, the form of the fossæ, the fatty capsule, the perirenal fascia, and I hold much more than is generally believed, by the maintenance of normal intra-abdominal pressure. In passing, I believe variations of this are frequent in the female, but normally completely unknown in the male. The vessels and nerves forming the hilum also play a part, as does also its peritoneal associations.

The fixations are: (1) the fatty capsule; (2) the vessels and nerves; (3) partial covering of peritoneum.

Lungs. The right lung is larger and heavier than the left and is situated higher in the thorax for two reasons: because of the presence of the large lobe of the liver and in the absence of the heart. Thus the limits of the organ are: in the nipple line it reaches the sixth rib, and in the posterior scapular line the tenth rib. In the case of the left lung its lowest limit is the upper border of the eleventh rib. It is most important to remember those simple anatomical points.

Thus one can risk perforating the tenth intercostal space on the right side without, in the majority of cases, involving the lung, but one cannot go higher with safety than the eleventh on the left side.

Pleura. The lower border corresponds in the nipple line with the eighth rib. In the midaxillary line the tenth rib on the left side and the ninth rib on the right. In the posterior scapular line with the twelfth rib, and in some cases with the

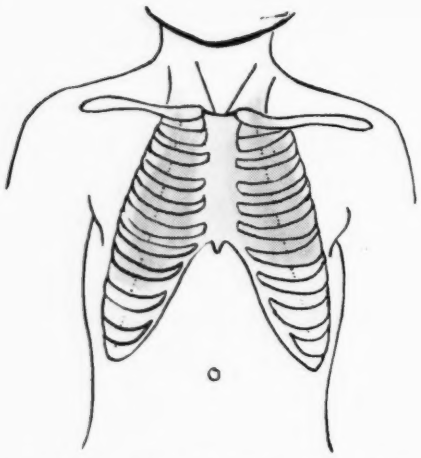

Fig. 3. The relationship of complemental pleural space.

transverse process of the lumbar vertebra. The supplemental or complemental pleural spaces are best shown in the following diagrams (Fig. 3).

Intercostal space. Between the costal cartilages and the angles of the ribs you have the skin, overlying muscles and fascia, external intercostal muscle, intermuscular areolar tissue, with arteries, veins, lymphatics and nerves, internal intercostal muscle, endothoracic fascia.

It is to be particularly noted that posterior to the angles of the ribs, the intercostal vessels and nerves cross the intercostal space obliquely. This is probably the most important point to be noted because to avoid injuring the structures the needle carrying the superior suture must perforate the intercostal space anterior to the angle of the rib; otherwise there is danger that these structures may be injured. If the proper needle be used, however, that danger is very remote, but in any case this space should not be utilized.

PHYSIOLOGY

It has been observed that the kidneys under normal circumstances have a definite anatomical position. Their disposition in that region is such that their attachments and relationships with their surroundings allow of a certain amount of definite and unrestricted movement. The manner in which they are anchored and the presence of a specially disposed and relatively mobile fatty capsule protects them from any undue external influence of moderate severity. The presence of this shock-dispersing elastic casing, as the fatty capsule might be called, allows unrestricted intrarenal movements which unquestionably occur during digestion and other modifications of the system generally. Being situated in close contact with the main muscle of respiration, the diaphragm, they are never at complete rest. Recognizing the fact that they are peculiar inasmuch as they may be regarded as being both secretory and excretory, very considerable variations in their volume are constantly occurring.

Intrarenal movements are these which occur during variations in blood pressure, digestion, stimulation of the sympathetic, and in the female during menstruation and pregnancy.

Intrarenal movements have been demonstrated by Roy and Cohnheim, using an oncometer. By means of this method it has been shown conclusively that the volume of the kidney varies rhythmically and continuously. Such being the case and recognizing the fact that the capsule of the kidney is in molecular continuity with the renal parenchyma, these intrarenal movements exert a certain amount of movement, slight though it may be, of the organ in relation to its surroundings.

Extrarenal movements are those which occur in virtue of its anatomical position and may be classified as: (1) respiratory, (2) visceral, (3) vertebral, and (4) muscular.

As it is in relationship both directly and indirectly to the main muscle of respiration, the diaphragm, a certain amount of mobility is created with each respiratory act. The intercostal muscles probably exert a slight secondary influence.

The right kidney is probably the more mobile of the two because of its close relationship to the liver. Mobility in the case of the left is not so marked because while it is more highly placed and has an extensive and intimate gastric relationship, its diaphragmatic association is weaker and there is a tendency to increased stability due to the anchoring effect of the tail of the pancreas inferiorly, the comparatively immobile spleen, and the shortness of the left renal artery. The peristaltic action of the large and small intestines have a definite effect.

In all the movements of the vertebral column there is a definite degree of renal movement probably more pronounced in full flexion.

Muscular action is most marked in people who use their lower limbs with the trunk more or less fixed such as bandsmen, who, by the use of the lower limbs with the trunk rigid, bring into active use the iliopsoas muscle. Indirectly through violent action of the latissimus dorsi, by fascial attachments, renal movements are produced.

Any operation which may be devised must, to be successful, take fully into account those two sets of movements with their subdivisions. In the case of the intrarenal movement probably an eighth of an inch is approximately the average extent of change of position. Extrarenal movement has been definitely determined to vary between one half and one and a half inches. Movements of the intrarenal type produce a general movement of the whole organ due to a uniform expansion within its capsule. The greatest range of extrarenal movement is the result of respiration, that due to movement of the vertebral column is a side-to-side act and anteroposterior, while that due to adjacent visceral peristaltic action is of the rotatory type. Movement due purely to muscular action is vertical as the organ merely slides up and down within its fascial tube.

ETIOLOGY

Abnormal conditions may be congenital or acquired; some are undoubtedly of congenital origin and are not manifest until some untoward circumstance reveals their existence. Probably the best known example is that of hernia, it now being an accepted fact that the congenital sac may remain dormant until, by an accident of circumstance, a piece of bowel or omentum finds its way into the mouth of the sac which has been lying waiting for it, so to speak, and a hernia is thereby produced.

True abnormal renal mobility is in all likelihood due to the same cause; a true floating kidney is almost certain to be found to be of congenital origin. Bearing these possible facts in mind one may classify the cases as: (1) congenital, (2) hereditary, (3) sex, (4) acquired.

The congenital class may be due to (a) presence of meso-nephron, (b) laxity of capsule, (c) deficiency in depth of renal fossæ, (d) deficient symmetry of body, (e) increase of length of blood vessels and ureters, (f) failure to assume normal position during development, (g) deficiency in nerve supply, and (h) spinal curvature.

As to heredity in all probability there are families who are predisposed to the development of this condition, just as there are families who are, apparently, predisposed to certain other diseases. That predisposition may be the result of one of many factors, regarding which, at present, we know nothing.

Billington records a series of cases in which he has operated upon several members of the one family. I cannot record a similar experience to date, but I can record a similar state of affairs associated with carcinoma of the breast, appendicitis, and hernia. In one case I removed the mother's appendix and within one year removed those of her three daughters and son, all being of the acute catarrhal type.

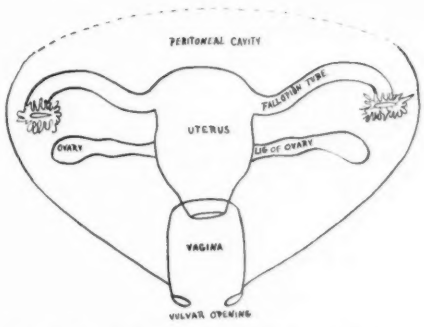

Fig. 4. The continuity of peritoneal cavity with external atmosphere in female.

Regarding sex, it is agreed by all investigators that the proportion of cases of abnormal mobility of the kidney is vastly greater in the female than in the male. Why should this be so? Many causes have been enumerated to account for it, as follows: (a) tight lacing, (b) repeated pregnancies, (c) transitory hyperemia which accompanies menstruation, (d) anatomical peculiarities. All these factors may play a part, in many cases a very important part, but I cannot say that even in the presence of congenital deficiency they explain more than a small proportion of the cases which are met with.

I believe that the intra-abdominal pressure in the male is greater and more constant than that in the female, and while it may undergo variations in both sexes, the variation is always greater in the female, because the peritoneal cavity is in direct communication via the fallopian tubes with the external atmosphere. Thus, the intra-abdominal pressure in the male is 760 millimeters of mercury whereas it may or may not be so in the case of the female. When that fact is taken into account along with the anatomical formation of the female renal fossæ I hold we have a very feasible explanation for the greater frequency of the condition in the female as compared with that in the male.

In fact, the peritoneal cavity in the female may be compared to the lungs in both sexes, as the same molecular continuity holds good in both. The accompanying diagram demonstrates in a clear manner the anatomical continuity of the female peritoneal cavity with external atmosphere (Fig. 4).

In the acquired class the condition may be due to

1. Chronic cough,
2. Constipation,
3. Cecal distention,
4. Debility,
5. Spinal curvature,
6. Renal enlargement due to—
   (a) Calculus,
   (b) Hydronephrosis,
   (c) Pyonephrosis,
   (d) Cysts,
7. Enlargement of adjacent organs—
   (a) Liver,
   (b) Suprarenal capsule,
   (c) Spleen,
   (d) Gall bladder,
   (e) Stomach,
   (f) Colon,
8. Pelvic disease through the media of adhesions to adjacent structures,
9. Trauma.

Trauma may be one or all of three varieties, or all three combined, but before any of them can be effective there must be a congenital predisposition which may be partially or completely developed. If this predisposition does not exist then there is every likelihood that the trauma will rupture the organ in preference to displacing it.

I would divide trauma into two classes, that of intra-abdominal origin and extra-abdominal origin:

(a) Intra-abdominal
   1. Straining due to constipation,
   2. Tumors of adjacent viscera,
   3. Colonic displacements,
   4. Traction exerted by adjacent structures,
   5. Renal tumors,
   6. Renal calculi,

(b) Extra-abdominal
   1. Sudden direct violence—
      (a) Blows,
      (b) Strains,
      (c) Falls,
   2. Gradual,
   3. Occupational — anything which may cause continuous or excessive action of the iliopsoas muscle.

OPERATION

The essentials of the operation are:

1. Restoration of the kidney to its normal anatomical position and relationship.

2. Re-establishment to its normal mathematical and anatomical position, therefore, restoration of its normal line of gravity, therefore, less encouragement for it to assume an abnormal position.

3. Restoration of, and fixation to, its normal position by a method in which the normal intrarenal and extrarenal movements are neither modified nor prohibited.

4. No interference with the kidney tissue.

5. Restoration of the renal capsule to its normal relationship to the kidney when the sutures are tied.

6. All sutures employed in the fixation must be associated with structures which are in normal relationship with the organs and move normally with it.

7. Any procedure employed must fix the superior renal pole in its normal position and the renal vessels seen to be at a right angle with the aorta and inferior vena cava respectively.

The object of the practice of any operative procedure is to restore the abnormal part or organ to its normal position and condition. In any candidate for surgical interference, the pathological conditions which exist present indications for operative interference which indications may be absolute or relative, and the same may be said of contra-indications.

In the case of abnormal mobility of the kidney the indications for operation may be divided into the primary and secondary, or absolute and relative.

Primary indications are:

1. Pain,
2. Tenderness,
3. Enlargement,
4. Fixation of the kidney in an abnormal position,
5. Rotation of the kidney,
6. Intestinal obstruction,
7. Hydronephrosis,

Secondary indications are:

1. Nervousness,
2. Digestive disturbance,
3. Intermittent pain,
4. Recurrent pain,
5. Occasional discomfort,
6. Gynecological reasons—
   (a) Dyspareunia,
   (b) Dysmenorrhea,
   (c) Metrorrhagia,
7. Marriage,
8. Athletics,
9. Travel.

Dr. E. L. Keyes has written an excellent paper on the management of calculi in the solitary kidney but no mention is made in that paper, or in any other publication which I have read, regard-

ing the management of abnormal renal mobility in the solitary kidney.

Recently I was asked to see a case in which the left kidney had been removed some time previously. The patient was far from well and the right kidney was enlarged, mobile, and tender. In addition to her renal symptoms she was in poor general health and there was very pronounced general enterovisceroptosis. Realizing that the operative dangers were increased considerably on account of the absence of the left kidney, I decided to take the risk and operation was proposed, accepted, and accordingly performed with only very slight disturbance after operation, and an ultimate happy result. I, therefore, do not, other things being equal, regard the absence of the opposite kidney as a contra-indication to operation. but it must be remembered that should a surgical tragedy occur, such as tearing of the kidney substance with uncontrollable hemorrhage or tearing of the vessels themselves, then a fatal result is most definitely assured.

Preparation of patient. It is always advisable to have the patient resting in bed for 48 hours previous to operation, if at all possible. During this time the patient's general condition should be carefully examined and the total quantity of urine passed in 24 hours ascertained. The operative area is thoroughly washed with soap and water, cleansed by turpentine, and then with spirit and, finally, a 1:40 carbolic compress is applied but no gutta percha tissue is ever used.

This dressing is changed every 12 hours, and 2 hours before operation it is finally changed for a compress rung out of 1:20 carbolic solution which is applied and which is removed on the table when the area is finally swabbed with spirit. During this time the bowels are emptied by the use of purgative and an enema. The diet is liberal and nourishing and of a variety which is easily digested. No solid food is given for 6 hours at least prior to operation. Half an hour prior to operation a quarter of a grain of morphia is given and a two-hundredth grain of atropine.

In the early operations the large curved sharp pointed needle of Doyen was used, which served the purpose well, but I always felt that considerable damage might be caused by it. I, therefore, decided to design the needle which I now invariably use, and which is now described (Fig. 5).

Fig. 5. Transpleural nephropexy needle.

TECHNIQUE

This is most conveniently described in stages.

First stage. At least 48, probably 72, hours should elapse between the admission of the patient and the performance of the operation, and should any suspicion of any heretofore undiscovered constitutional condition present itself the operation must be delayed until matters are righted. The pre-operative period is to be occupied by rest, the amount of urine voided in 24 hours estimated, and the alimentary canal cleansed and dressed in the usual manner.

Second stage. The anesthesia invariably employed by me is chloroform. I am quite aware that it is not the popular anesthesia of today, but I have never had any reason to be dissatisfied with it and I am still a firm believer in the views which were so ably and persistently expressed by my distinguished teacher, the late Professor Sir William Macewan. The anesthesia is administered by the ordinary simple open mask and seldom has any difficulty been experienced. The patient is placed upon the operating table, lying flat on the back with the lumbar air pad in position ready for inflation. Anesthesia being complete, the patient is turned upon the side opposite to the one being operated upon, the thighs flexed upon the abdomen, and a sand-bag placed against the shoulder blades. By this means they are steadied in the desired position for operation. The inflation of the lumbar pad increases the costovertebral angle.

Four towels wall off the operative area and over them is placed a large sheet with an opening large enough to permit of the operation being performed.

Third stage. The line of incision is transverse and runs from the anterior border of the erector spinæ directly forward ½ inch below the twelfth rib for a distance of from 3 to 6 inches, according to the size of the patient. With the first stroke of the knife, skin and subcutaneous tissues are incised. The deeper tissues are now exposed and the fibers of the latissimus dorsi muscle are now recognized. In many instances they may be separated and the posterior border of the external oblique muscle is reached, which is usually displaced forward.

As the result of the foregoing manipulation a quadrilateral space is formed, bounded posteriorly by the anterior border of the erector spinæ and quadratus lumborum muscle, anteriorly by

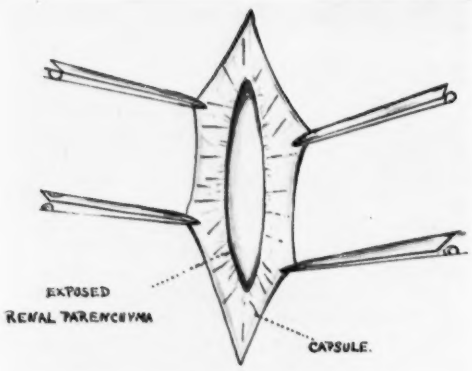

Fig. 6. The capsule of the kidney split and the renal cortex exposed.

the posterior border of the external oblique muscle, and superiorly by the inferior border of the twelfth rib, and inferiorly by the iliac crest. The floor is formed by the internal oblique and the lumbar aponeurosis. In this space will frequently be observed the twelfth dorsal nerve and sometimes the iliohypogastric nerve. They are, if at all possible, carefully avoided.

The lumbar aponeurosis is divided transversely and also any of the fibers of the internal oblique, if separation is found difficult. The lumbar fat and perirenal tissues are now freely exposed and the position of the kidney determined.

Fourth stage. During the previous stage of the operation the lumbar air pad has been gradually inflated, and the inflation is continued until the kidney makes its appearance in the depths of the wound. The kidney is steadied by being firmly grasped in the hand, if possible, and also by pressure forceps grasping the perirenal fat.

As a rule I do not deliver the kidney on to the surface of the wound, as I find I can, by means of steadying it in the manner described, clear its convex surface and incise the capsule with ease (Fig. 6).

The organ having been carefully examined and no tumors, cysts or stones found, the convex surface is now cleared of all perirenal fat, if such should be present. I do not clear the perirenal tissues to any greater extent than is necessary. Clearance having been effected, the capsule is now incised from the superior to the inferior pole. In the majority of cases the capsule can be easily incised without involving the renal substance but, if any difficulty is experienced, the incision can be commenced at the lower pole and continued upward. A pair of blunt pointed dressing forceps is used so as to raise the capsule from the cortex but as a rule this is entirely unnecessary.

I have found the capsule separator of great help in many cases and I now invariably employ it, as it is a sure prevention against injury to the renal cortex. The instrument has no sharp bends, it is completely rounded and blunt pointed; therefore it cannot injure the renal tissues. After completion of the incision the edges of the incision are grasped by pressure forceps and the handle of the knife or a blunt director separates the capsule on either side of the incision for a quarter of an inch so that from ½ to 1 inch of cortex is exposed, the object being to produce adhesions between it and the surrounding tissues when the retention sutures are tied (Fig. 7).

Seven sutures are now introduced. Most surgeons use silkworm gut. I use nothing but No. 3 catgut, each suture being one foot in length. The superior suture is first introduced at the superior extremity of the split capsule. The suture is introduced so that a small area of capsule is included round which two turns of the suture are made, but is not tied because I believe it is unnecessary. Further, if the knot should be too tightly tied there is a possibility of a localized area of necrosis developing and the purpose for which the suture was utilized is defeated.

The lateral sutures, which are of the mattress variety, are introduced three on each side, 1 inch apart.

Fifth stage. The first suture to be dealt with is that of the superior pole. All sutures having been introduced, the superior ones are taken and threaded into the eyes of the renal needle which, when operating on the right side is taken in the right hand. If the kidney has been delivered on to the surface of the wound it is now replaced into the abdominal cavity, the inferior pole being replaced first, and the left hand of the operator is introduced with the palmar surface approximated to the internal surface of the thoracic wall. The needle is guided between the second and the third fingers to the tenth intercostal space and at the junction of its middle and posterior thirds the needle is made to perforate the space and its point appears beneath the subcutaneous tissues. A touch with the knife and the sutures arrive on the exterior and are then withdrawn from the needle. The delivery of the point of the needle on the external surface of the thoracic wall is accomplished with the greatest ease by simply separating and incising the fascial planes once the point is in the intercostal space and depressing the handle. The needle is now withdrawn and the

ends of the superior sutures held by an assistant who has secured them by pressure forceps. The lateral sutures are now threaded on to a round needle and left untied, and this suture is made to transfix all the tissues up to the superficial layer of the subcutaneous tissues, the skin edge being gently retracted. They are passed so that when tied they are at an angle of 45 degrees with the renal capsule. The anterior sutures are, as a rule, first placed in position. After all have been passed, the superior pole suture ends are threaded on to a round needle and stitched into the subcutaneous tissue and securely knotted. A single continuous catgut suture of the skin wound completely closes the wound in the subcutaneous tissues and the skin.

The lateral sutures are now tied and the kidney is thus secured in its normal position. It will be observed that no suture is tied outside the wound, which, on the completion of the capsular anchoring and the approximation of the muscular and facial planes, can be completely closed.

The lumbar air pad is now gradually deflated and the muscular and facial planes are closed by interrupted sutures. The skin, by interrupted cutaneous or subcutaneous sutures. Very often an anchor dressing is applied, which is more comfortable than a collodion dressing. A firm pad of cotton wool is applied to the abdomen and a bandage applied.

Sixth stage. Immediately on the completion of the operation, 0.5 cubic centimeter of pituitrin is given and repeated once every hour for 6 hours, and a rectal saline composed as follows:

Glucose	½ ounce
Aspirin	20 grains
Potassium bromide	30 grains
Saline	10 ounces

is given and repeated in 6 hours if necessary. The patient is placed lying flat on the back for the first 24 hours. They may, if they will, lie on the side operated on, but not on the sound side.

The morning following the operation a flatus enema is given which is repeated once every 24 hours until the bowels act naturally. Commencing 24 hours after operation 1 grain of calomel is given every 8 hours until the bowels move. As a rule this happens not later than the third day.

This treatment has given very satisfactory results; in fact, many of the patients have hardly experienced any postoperative discomfort. Approximately 20 per cent have in addition required one hypodermic of ¼ grain of morphia, but as a rule it is neither requested nor given. When morphia is given it is dissolved in a 25 per cent solution of magnesium sulphate. By this method its efficiency is much enhanced and the possible ill effects are in most cases entirely obviated (synergistic analgesia).

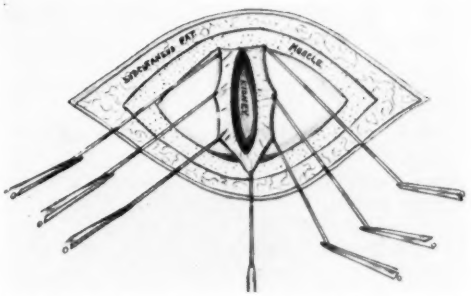

Fig. 7. The renal cortex exposed and sutures in position in renal capsule.

Seventh stage. At the end of the eighth postoperative day the wound is inspected, the anchor dressing removed, and the line of incision sealed with collodion. The abdominal pad of cotton wool is replaced and bandaged firmly. A course of massage is now commenced, the muscles of the anterior abdominal wall being first treated. After the first 3 days the whole body is massaged. The advantage of this treatment is that the muscle tone of the abdominal muscles is largely restored, the treatment in almost every case fatiguing the patient just sufficient to induce natural restful sleep.

Rest in bed is given for 21 to 28 days, after which time has elapsed they are allowed up for longer intervals daily. By the end of the sixth postoperative week they are, as a rule, fully restored to their usual habits.

Belts, trusses, or supports are as a rule not advised. If the operation has been successfully performed, they are unnecessary. They serve only to remind the patient of an unhappy past, hamper the action of the muscles, and maintain the loss of tone, and are a source of general discomfort and discouragement to the patient. If any sense of weakness is felt, which is unusual especially when the transverse incision has been employed, they may wear an ordinary 6 inch bandage or a woolen body belt, but the majority are only too glad to dispense finally with any apparatus they may have worn prior to operation.

RESULTS

The final decision as to the efficiency of any method of treatment is based upon results. Results are observed more promptly and definitely in the wake of surgical intervention than in any

other form of treatment. The success or failure, partial or complete, of any form of surgical procedure is most accurately assessed by determining the number of patients who have been submitted to operation and the percentage of which, as the result of such treatment, have been able to resume their usual mode of life or occupation. Further it is assessed by the length of time required to obtain that more or less perfect result, which infers that they do not require to restrict themselves either socially, commercially, or athletically, and that they do not require to wear any form of artificial support. A patient who fulfills these conditions can be justifiably classified as a cure.

The 40 patients forming the subject matter of the present paper are classified as follows: 39 can be held to have fulfilled these conditions; the last case may, but it is at present too early to pronounce final judgment.

In assessing operative results, the following factors have to be considered:

1. Condition of the scar as regards
   - Appearance.
   - Sensibility.
   - Integrity.
     - a. Presence of keloid,
     - b. hernia,
     - c. deficient muscular action,
     - d. contraction.
2. Position of replaced kidney.
3. Restoration of normal function of replaced kidney and therefore, disappearance of renal abnormalities, which may have been present prior to operation.
4. Disappearance of all constitutional symptoms which were present prior to operation.

To place a true value on these results a fixed period of observation is essential. Many of the patients operated on have been observed for periods of time varying up to 9 years from the date of the operation but as a working rule it might be said that any case in which the organ remains in its normal position, and in which there is no recurrence of any of the symptoms for a period of 5 years from the date of operation may be classified as a permanent cure.

All the patients in the present résumé have been examined since the operation and the result to date is all that could be desired. In first case operation was done in 1914 and, while I have not seen patient personally for some years, her medical attendant has informed me at this date that she has remained perfectly well, has borne several children, and has not had the slightest recurrence of symptoms since her operation.

The remaining patients have all so far complied with the requirements laid down in the first part of this section. Several patients in whom the nervous symptoms were the most prominent clinical factors have reported complete recovery and now lead normal lives.

To date so far as I know, there has been no recurrence of the condition, or of the symptoms, and no postoperative pain or discomfort. The fact is substantial proof that the laws and rules of physiology have been surgically correctly interpreted. That the operative procedures employed have not only restored the kidney to its normal anatomical position, but they have also been successful in replacing it in that position in a condition whereby it is enabled to resume its normal functions, unfettered by any artificial restrictions and with its anatomical surroundings unchanged. That it is in that condition post-operatively is, I believe, sound proof of the correctness of the principles upon which the operation is founded and the scientific accuracy of the operative technique which has been, and is, being employed.

CONCLUSIONS

The only description of this operation which I have seen is in Maylard's *Practice and Problems of Abdominal Surgery* and in that article the original technique is described in detail.

The present investigation has confirmed the original principle set down by its author, namely, that to be successful the whole convex border of the organ must be fixed, and especially the superior pole. So far as I know this is the only operation which fulfills that requirement.

While there is no doubt that abnormal renal mobility does occur in the male, it is questionable if it ever occurs to the same marked degree or so frequently as it does in the female. The view advanced to explain this sex peculiarity may ultimately be found to be the one, if not the only, principal cause of true renal mobility and that true renal mobility is practically confined to the female.

While many well known surgeons are adverse at this present date to employ general anesthesia as a diagnostic aid, I submit that in at least 10 per cent of my cases a diagnosis would not have been arrived at without its employment. By its use complete muscular relaxation is obtained, the various abdominal viscera can be palpated through the abdominal wall and any viscus the support of which is directly or indirectly in any way deficient can be displaced from its normal position in a manner and to an extent impossible by any other diagnostic procedure.

Radiography and pyelography are useful, but radiography with the present technique is unreliable. I have stated that to date I have not employed pyelography as a diagnostic aid, my main reason being that one of the many recognized contra-indications to the employment of that method is almost constantly present, namely: a marked supersensitive patient, and there are others which, in my opinion, outweigh any advantage which the method may possess as a diagnostic aid in this particular condition. There is, however, one condition in which it is of real value and that is the ectopic kidney. It certainly places the diagnosis of that condition beyond doubt.

During the progress of this investigation, a case of solitary kidney was met with. No precedent could be found indicating that the operation had been previously performed in such a condition, as has been stated. After fully considering all the possibilities, it was decided to perform the operation, as it is held that the operation in no way interfered with the actual kidney substance, and therefore is very unlikely to modify the renal function. The result has justified the theory, and so far as I can determine no reluctance need be shown in performing the operation which in this case produced the desired effect.

The fundamental principle remains unchanged. All investigations to date have gone to prove its scientific accuracy, but the method of accomplishing the operation has been modified to a certain degree. The needle originally used served its purpose but the instrument now employed is believed to possess distinct advantages, mainly that it is unbreakable, its curve is anatomically correct, and, being blunt, it can do no damage; therefore concealed hemorrhage or severe damage to the pleura or lung is effectively guarded against.

The transverse incision possesses the same advantage here as elsewhere and by its use not the slightest pulmonary embarrassment or complication has ever been experienced.

It has not been found necessary to deliver the kidney on the surface of the wound and by refraining from this procedure surgical shock of any degree has seldom been observed. The use of catgut has obviated the removal of stitches and allowed immediate and permanent postoperative closure of the wound which is very desirable.

The success of the operation has been shown by the ease and safety by which it can be performed, but the conclusive proof of its justification is demonstrated by the disappearance permanently of all signs and symptoms and the absence of recurrence, and its entire safety by the absence to date, of mortality. That the sympathetic can, and does, exert such a powerful influence over the patient is clearly shown by the disappearance after operation of all nervous symptoms.

To my late friend and Chief Dr. W. D. Macfarlane, I desire to record my undying gratitude as, without his help, guidance, and encouragement at all times, this work, such as it is, would not have been completed. To my friends Drs. Reid, Waddell, and Wilson, for their assistance at all times I am truly grateful. Lastly to Mr. Boot for the beautiful diagrams I gratefully offer my most sincere thanks.

As the result of Maylard's pioneer work an operative procedure has been placed in our hands which to date has proved mortality free and by its results proved to be scientifically sound. By its use a certain proportion of the community has been converted from a life of chronic invalidism to a sphere of usefulness and social activity, and for whom, prior to the operation, life held no joy.

CHONDROSARCOMA

The Relation of Structure and Location to the Clinical Course

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Voluntary Assistant in the University Surgical Clinic of Prof. Peter Walzel

AMONG the cases of bone sarcoma which have been treated during the past 5 years in the Graz Surgical Clinic, 9 cartilaginous structures were found. These have been verified pathologically, and even though 2 were so far advanced at the time the patients entered the clinic that they presented more of a pathological than a clinical picture, the cases are of value in a consideration of the prognosis and treatment of the condition. Although the histological structure in 3 of these tumors is such as to allow of inclusion with the chondrosarcoma, other factors would place them in the group of relatively benign chondroma. They are discussed here with the sarcomas, however, because of the histological picture, which may be the same in the clinically benign form as in those cases in which clinical and X-ray examinations demonstrate a pathological invasion. They are included also because the course of chondromyxoma of the small bones of the hand and foot is somewhat uncertain, the outcome depending on whether or not treatment has been given, and, if given, whether curettage has been complete. The 4 remaining cases contribute data as to the results in attempts to effect cures in outspoken malignant chondrosarcoma of bone. The results in these 4 cases may be considered in the light of (1) the histological structure, which permits one to judge, on the basis of statistics, as to prognosis; (2) the anatomical location—an important factor determining not only the surgical accessibility of the growth but also the association of the growth with numerous connective tissue and cartilaginous structures, the presence of which in joints provides the embryological soil from which these growths are believed to arise, just as they arise from the soil of later cartilaginous metaplasia, as in the sternum; and (3) the time after operation before recurrence, the variability and uncertainty of which, somewhat paradoxically, is the surest criterion as to prognosis.

A review of the records of such tumors from the files of a large surgical institution which deals chiefly with the diagnosis of malignant conditions and the most effective treatment of them, discloses a typical clinical picture. The value of a case report depends on the extent and detail given as to the clinical, radiological, and pathological examinations, so that conclusions here given depend on the evidence shown in the records and are based on the extensive knowledge of bone tumors that has accumulated in recent years.

The compilation of the American Registry of Bone Sarcoma has done much to clarify the diagnosis of such tumors. The extensive files of the Registry with its complete records of examinations in the cases included in the Registry lend authority to its statistics. From the classification of the Registry, Geschickter and Copeland have evolved not only a histological picture but a description based on the embryological origin of the tumors and their genetic composition. In this paper, therefore, no attempt will be made to discuss the subject of chondrosarcoma in general, but we shall endeavor rather to discuss several cases in the light of what is already known. Conclusions are drawn chiefly from these. A summary of the histological relationships and their significance, factors in prognosis, indications for, and the effect of, treatment is presented with each case.

Case 1. The patient was a laborer, 20 years of age. A year before entry, he had squeezed the fifth finger of the right hand. The swelling did not entirely subside, but gradually assumed a firm character. Patient thought that this might be due to his habit of carrying bottles with this finger. Examination showed a hazelnut sized tumor of firm consistency in the volar aspect of the middle phalanx, limiting motion. X-ray report: "Cystic expansion of the middle phalanx by a central bean sized area of resorption, with sclerosed borders, that involves the proximal two-thirds of the bone shaft—a chronic inflammatory affection of bone, probably tuberculous."—Prof. Leb. Curettage for biopsy demonstrated a bone cyst, the gelatinous, blackish gray content of which showed under the microscope "mucinous tissue with typical star shaped cells, as well as remnants of bone tissue attacked by osteoclasts, in addition to osteoid borders on the bone areas—myxoma with bone destruction."—Prof. Beitzke (Fig. 1). The specimen was described by Prof. Carl Sternberg as "myxosarcoma, originating either in joint tissue or in bone." (Prof. Sternberg's comment that the tumor may have originated either in joint tissue or in bone is noteworthy.) Disarticulation of the finger was performed through the carpophalangeal joint. Eighteen months following discharge, the patient showed no local recurrence or lung metastases.

This case is an example of phalangeal enchondroma, histologically malignant but clinically benign, particularly in the light of operative curability following early and complete removal in the absence of similar structures in other bones.

The giant cells may here be regarded as secondary agents in the destruction of bone by the mucinous tissue, but their appearance and location in the section (Fig. 1) suggest a common origin for the giant cells and for the myxomatous tissue containing the giant cells. This view is supported by the fact that the skeletal location of chondrosarcoma and benign giant cell tumor closely corresponds.

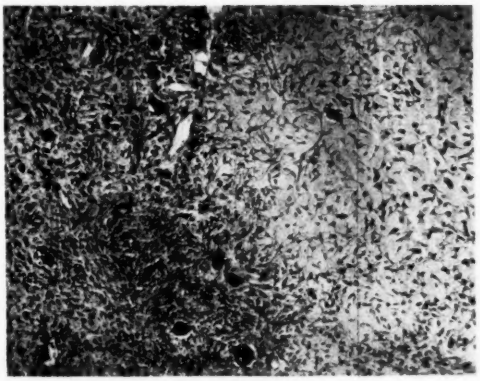


Fig. 1. Myxoma with bone destruction, Case 1.

CASE 2. A laborer, 19 years of age, had noticed a gradual enlargement of the small toe of the right foot during the course of a year. He had had no antecedent infection or injury. Examination revealed a resistant, indurated swelling of the small toe, the size of a hen's egg. Amputation of the toe with complete removal of the tumor was done. Pathological diagnosis: "Terminal phalanx completely replaced by a plum sized lobular tumor mass of cartilaginous consistency, surrounded by a capsule. Microscopically composed of nodules, divided by connective tissue septa and composed partly of fibrillar and hyaline intercellular substance, and of cells which are in part similar to cartilage and encapsulated, and again are of spindle shape and of varying size. The cells are present in greater numbers than in normal cartilage. The tumor is sharply separated on all sides from surrounding fat and connective tissue by a completely intact capsule, and approaches in no place the edge of the incision—chondrosarcoma." Postoperative radiation was carried out for a month. Attempt to trace patient 4 years after operation was unsuccessful.

Unfortunately, the slide was not preserved. The occurrence in a phalanx and the sharp, though fibrous, encapsulation, suggest an enchondroma. But here the transition of cells to cartilage tissue seems to occur without a myxomatous medium, although the cartilage cells present are nevertheless of an embryonic type. The tumor reached a comparatively large size in the short time of a year, and, as will be discussed later, this rapid growth corresponds to the absence, or small amount, of myxomatous tissue. Whether a typical phalangeal chondromyxoma existed before the assumption of rapid growth can not be determined. Of further interest is the total destruction of the surrounding capsule of cortical bone.

CASE 3. A boy, aged 14 years, had noted, 3 years before entry, that a small stationary tumor, which had been present for an indefinite time on the back of the left hand, began to grow. The growth made the use of the hand painful. The onset of increase in size was not connected with injury as far as patient remembered. Examination disclosed a hard, nut sized tumor in firm connection with the second metacarpal bone. X-ray film (Fig. 2): "Aspects of a chondromatous degeneration of the bones of the hand, with cartilaginous exostoses and endostoses. The largest exostosis arises from the lateral border of the shaft of the second metacarpal. The cartilaginous exostosis is about the size of a plum, has an uneven border, and indents the shaft of the neighboring third metacarpal from the palmar aspect. The upper end of this growth is not sharply defined, so that operative removal seemed indicated to circumvent a possible malignant degeneration of this part. In the proximal phalanges of the third and fourth fingers are transparent bean sized areas, such as may be produced by enchondromas. The bone shafts are expanded and broadened by one-third of the normal diameter. Foot bones are negative."—Prof. Leb. A glistening, nodular cartilaginous tumor, encased, except for the upper tip, in a thin, grayish-white capsule of the consistency of shrimp-shell, was removed by chiseling through this attachment to the second metacarpal and curetting out the entire mass (Prof. Walzel). Postoperative X-ray picture showed small scattered bone splinters in the operative wound bed. The histological section was that of a typical chondroma (Fig. 3).

This case occupies a position midway between the first two. It resembles the first in that its structure is myxomatous and is divided into lobules by connective tissue septa, and in that it is sharply circumscribed by a bony capsule. It resembles the second in its tendency to penetrate and destroy the capsule at one point. It is not characteristic of a typical cartilaginous exostosis, or osteochondroma, because of the overwhelming predominance of myxomatous cartilage and the complete bony encapsulation (except for the one point of penetration), as well as its diaphyseal location. It is reasonable to assume here that the areas appearing as enchondromas in the roentgenogram possessed the same histological structure as did the peripheral growth which was removed at operation. The relation of the peripheral growth to its capsule was the same as that of a typical central chondroma which grows against, and bursts through, its bony confines. It is illustrative of the course of a growing phalangeal chondromyxosarcoma unchecked by operative intervention, and it also is illustrative of the possible future course of associated phalangeal enchondromas. Although the patient lacked the gross stigmas of Ehrenfried's hereditary chondrodysplasia, often found as the background of multiple chondromatosis, the broadening of the phalangeal metaphyses is suggestive of this asso-

Fig. 2. Roentgenogram, Case 3.

ciation. That the operative removal was not radical allows room for the assumption that this "cortical chondroma" will recur. That a similar histological appearance is characteristic of benign phalangeal chondroma—myxoma contained in a cortical shell—brings out not only the fundamental similarity of chondroma and cartilaginous exostosis, but the justification for the term "cortical chondroma" for this tumor. It strengthens the view that the benignity of the central phalangeal chondroma is at least in part determined by its cortical shell, which, in the case of the myxoma arising in this exostosis, is not complete enough to check the mechanical tendency of this type of tissue.

Case 4. A housewife, aged 39 years. Her only previous illness was pleurisy 2 years before admission. Indefinite pains were noticed in the sternum 13 months previous to entry. For 7 months swelling over the sternum, slightly increasing in size, had been noticed. She had occasional light pain in the right axilla when working. Examination revealed a firm, round, somewhat elastic, tender swelling in the middle of sternum. The skin over the tumor was of normal texture and color and without attachment to the tumor. X-ray report: "Sternum differentiated only faintly because of high grade diminution of the calcium content. Beginning under the manubrium, the body contained scattered areas of transparency. Question of tumor

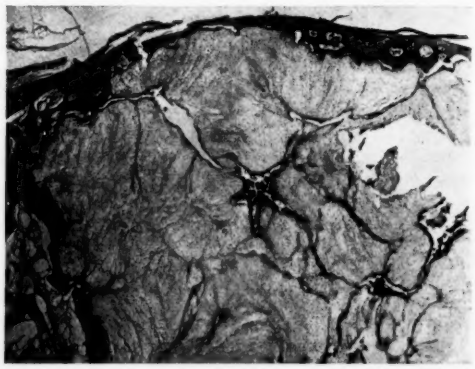


Fig. 3. Typical chondroma, Case 3.

or of tuberculosis. The lowest portion had a normal configuration." (Postoperative roentgenograms of the sternum gave the same findings.) Biopsy: the specimen was a gelatinous mass containing crumbly pieces of bone; the posterior sternal wall was reduced to paper thinness. Microscopic report: "Blood and numerous irregularly formed and growing cartilage cells in adjoining clusters—chondroma." Sternum resection was done April 3, 1933 (Prof. Walzel). "Incision was made over the manubrium sterni about tumor, which was the size of a goose egg. Division of cartilaginous ribs—second, third, fourth, and fifth—on the left. The left sternal margin was lifted and freed from its adhesions with the left pleura and pericardium. The tumor penetrated posterior wall, but did not infiltrate the pleura; the corresponding costal cartilages on the right were divided and the sternum was removed by chiseling just beneath the upper border of the manubrium." Microscopic examination of the specimen showed: "Cartilage tissue with occasionally widened cartilage cavities and scanty intercellular substance. Some areas contained many cells; the cartilaginous tissue infiltrated the bone and exhibited necrosis and hemorrhage: chondroma, with partial transition to sarcoma."—Prof. Beitzke (Fig. 4). A month later, two control X-ray pictures showed only the remainder of the normal manubrium. Patient discharged as healed, May 6, 1933. Three months later, another control showed only flaky calcium deposits in the region of the resection. Five months following discharge the patient entered again because of a firm, plum sized growth in the upper end of the operative scar. X-ray examination October 24, 1933, showed: "Oblique view of sternum, body resected; manubrium atrophic, with irregular contour and small area of bone destruction beneath the right sternoclavicular joint." Lung fluoroscopy: "Pyramidal uniform shadow of soft tissue opacity in the periphery of the left lower lung field." October 26, 1933: manubrium resection (Prof. Walzel)—separation of sternal portion of pectoral muscle. The tumorous protrusion corresponded to the right hand portion of the manubrium sterni. The right clavicle was divided at the junction of inner and middle thirds, and of the right first and second ribs, a finger's breadth from their manubrial attachment. Disarticulation of the left side of manubrium was done at junction with left clavicle and first and second ribs. Preparations showed chestnut sized tumor infiltrating the bone. Control X-ray examination confirmed removal of manubrium and portion of clavicle, as well as presence of egg sized shadow in the left lower lung field, of soft tissue density, having the appearance of a tumor metastasis, or

of confluent lobar pneumonia. November 26: Patient was discharged as healed. January 1, 1934, X-ray examination revealed: "Infiltration in the lower lobe of the left lung unchanged." Differential diagnosis lay between metastasis and organized remnants of the empyematous infiltration. Fibrous induration of both lung hili. Sternum and sternal third of right clavicle were absent. Flecks of calcification arose from the medial border of the first rib. Last control (May 8, 1934) showed a diminution in size of the opacity in the left lung field, which was then assumed to be the remainder of an interlobar pleurisy. Patient received radiation therapy following each operation.

The histological structure is again that of a chondroma, with transition to sarcoma. The myxomatous tissue is scarce and irregularly formed. The absence of evidence of a pre-existing tumor, and the fact that the recurrence bore the same microscopic appearance as the first tumor, speak in favor of a primary sarcoma. On the other hand, it seems to have been central in origin, and this, with the location in the sternum and the age of the patient, suggest an enchondromatous origin. However, it is questionable if an enchondroma can exist in such a location in a patient aged 40 years, and still remain benign. If this tissue is histologically that of a central chondroma in its early stage of development, it belongs to the division of secondary chondrosarcoma, in which the malignant change occurs soon and rapidly, or it illustrates clinically what is more frequently seen under the microscope—the uncertainty of the character of the primary tumor and of the prognosis. A further recurrence may almost be expected, although the patient is now without X-ray evidence of recurrence 8 months after the last operation.[1]

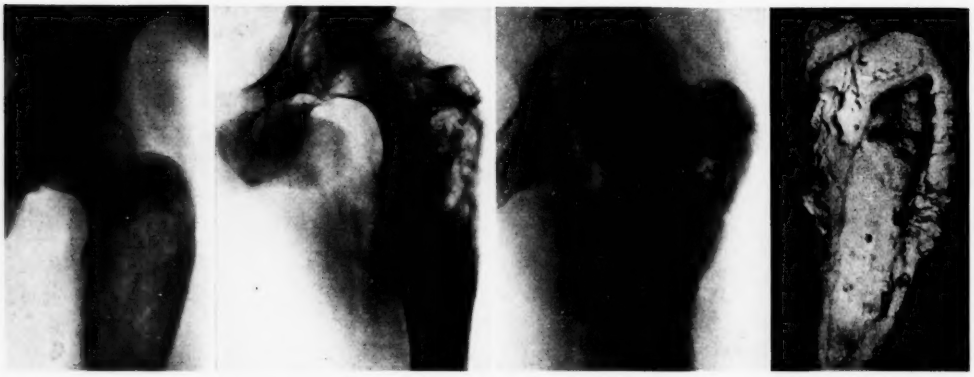
CASE 5. Soldier, aged 25 years, was admitted to the clinic August 10, 1933. Three months previously he fell against a stone during an infantry maneuver, striking the upper portion of the left thigh, producing a bluish swelling that lasted a week, and severe pain that at first prevented walking. The pain subsided somewhat, but since then persisted, radiating down toward the knee, at night especially severe. He has limped since the accident. Three months later an X-ray examination was made and the presence of an impacted fracture in the trochanter region on the upper border of what appeared to be a "myelogenic sarcoma" was reported. On admission to the clinic, the upper third of the femur was enlarged and tender. Hip movements were not limited, but painful. The first X-ray picture (Fig. 5a) bears the following description: "Lemon sized area of transparency beginning in the upper third of the femur shaft, extendin to the trochanter region. The bone is expanded to double its normal thickness at this point, about which periosteal apposition is present. There is no break in the continuity of the bone. The condition exhibits a slowly progressing central process of destruction

[1]The patient returned again in September, 1934, 11 months after the last operation, with a large recurrence in the operative scar eroding the proximal ends of the ribs, and with lung metastases. A particularly dense clouding of the left lower lung field confirms the impression that the infiltration seen during the preceding months was a pulmonary metastasis.

Fig. 4. Chondroma with partial transition to sarcoma, Case 4.

with periosteal new bone formation on the border. This circumstance speaks against a malignant tumor and may represent a benign, probably chronic, inflammatory area of destruction."—Prof. Leb. Curettage was done, August 19, 1933, by Docent Susani: exposure of the bone revealed a rough surface penetrated by cavities, within which there was gelatinous tissue. Complete curettage of this tissue was done and removed, with pus from a large central cavity. Patient was immobilized in a cast, and the wound healed after 2 months. X-ray treatment was given after operation. Microscopic report from curettage: "Network of hyaline connective tissue with calcium deposits, among which nests of cells were present, lying close together, with star shaped branching nuclei—chondrosarcoma."—Prof. Konschegg. This diagnosis was confirmed by Prof. Sternberg. X-ray findings a month following the operation: "Distention of upper portion of femur shaft to double the normal size. Central, irregular areas of destruction extended into the intertrochanteric region and at this point penetrated and destroyed the lateral cortex (operative defect). The medial cortex was thickened and strengthened through the newly formed periosteal apposition. In the direction of the bone shaft, there was periosteal reaction with strong newly formed bone. The expansion spoke for a slowly growing process of destruction. The perforation of the lateral cortex would nevertheless speak for a malignant process. Together with the marked periosteal reaction, the finding would not speak so much against a malignant tumor as in favor of relatively slow growth and benignity, This finding is given for giant cell tumor, osteochondrosarcoma, slowly growing hypernephroma metastasis, etc. Evidence is that of a differentiated, slowly growing malignant tumor."—Prof. Leb. X-ray pictures taken a month after this gave essentially the same result, except for a sharper circumscription of the transparent areas which were enclosed peripherally by a strong wall of periosteal bone. Following discharge, X-ray therapy was given.

Patient returned 5 months later, March 9, 1934, with a hard tumor the size of a grapefruit in the region of the great trochanter; this had appeared during the previous month and was associated with a renewal of radiating pains. Hip motions were limited and painful, thigh and gluteal musculature atrophic. X-ray, March 10, showed regeneration of the cortex which had previously been destroyed by the curettage, as well as two small bone defects on the lower border of the operative cavity (Fig. 5b)—a lateral view



a b c d

Fig. 5. a, First roentgenogram, Case 5; b, 7 months later; c, 2 months after b; d, photograph showing formation of spicules and perforations in the cortex.

showed further the sharp demarcation between shaft and intertrochanteric regions. Operation, March 16, 1934, by Docent Susani, showed gelatinous tumor masses filling the bone cavity and extending into the musculature, where they were surrounded by a firm, fibrous capsule. The tumor penetrated the remaining shell of bone in several places. Curettage was done and the bordering areas of sound bone were removed. Pathological report: "Dense connective tissue interspersed with necrosis and hemorrhages; among these nests of spindle and star shaped branching cells in an intercellular substance which stained blue with Van Gieson; in addition, cavernous bone showed transition to a reddish-staining homogeneous tissue to which numerous, large, irregular cells were applied. The bone trabeculæ themselves showed extensive regressive changes—osteoid chondrosarcoma" (Fig. 6). Following this operation, radiation treatment was done. On April 11, 180 milligrams of radium were implanted in the granulating wound cavity for 8 hours; the cavity had been prepared for this implantation by sewing the skin edges to the periosteal borders of the bone defect. X-ray examination, May 9, demonstrated a sharper demarcation of the area of bone destruction (Fig. 5c). In the following 3 months two or three small wound recurrences were removed by electrocoagulation, the pathological report of one showing patches of large, pale, round and spindle shaped cells and many thin blood vessels, associated with a pale blue staining tissue consisting of large round and star shaped cells, in the midst of which there was a pale brown fibrillar ground substance. Not definite whether it is chondroma or chondrosarcoma. The last X-ray film, June 19, gives a sharper demarcation of the defect in the lateral portion of the neck of the femur than before. In the region of the lesser trochanter are short bone spicules arising from the periosteum and extending into the vicinity of the medial side of the femur; these changes were demonstrable in the control picture taken a month before. The lungs showed no metastases.

(In a personal communication following the conclusion of this paper, Docent Susani informed me that he had successfully performed an acetabular disarticulation of the involved femur, and although the sarcoma had deeply infiltrated the medial musculature of the thigh, it had not extended above the level of the neck of the femur, and the lungs had remained roentgenologically free of metastasis.)

Figure 5d, is a photograph of the upper end of the enucleated femur, following its maceration, and shows the formation of spicules, and perforations in the cortex.

In this case, trauma may have lent growth impetus to a malignant tumor. The predominant chondromyxomatous structure, both histologically and roentgenologically, and the central location in the upper femur shaft, with the age of the patient, suggest an enchondroma or central chondromyxoma. That the symptoms associated with the injury fitted in with those present at the time a malignant tumor was found to exist—an interval of 3 months—favors the impression that a direct traumatic insult occasioned the development of a sarcoma from a benign central chondroma. This provides a good example of the failure of vigorous X-ray and radium therapy to check such a growth, although apparently limiting its progress through the stimulation of calcification and new bone formation. Of interest is the recent formation of bone spicules on the medial side of the femur. Although from the standpoint of structure, one might infer that the periosteum would be elevated only by the presence of malignant or inflammatory tissue, with the subsequent production of periosteal bone columns to support it, it is unusual to find periosteal spicule formation in association with a central, bone-destroying chondromyxosarcoma in the presence of a cortex roentgenologically intact. At operation, however, the myxomatous cartilage was found not only to have penetrated the cortex in a sieve-like fashion, but to have infiltrated the surrounding soft parts. This finding provides a commentary not only on the size of cortical defects necessary to X-ray

Fig. 6. Osteoid chondrosarcoma, Case 5.

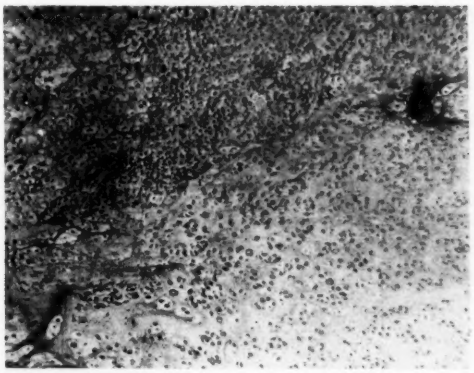


Fig. 7. Chondroma with transition to chondrosarcoma.

representation (2), but on the roentgenological translucency of the tumor itself. The reactive thickening of the surrounding bone tissue has been emphasized by Phemister, and there is little doubt that the advance of this reactive encapsulation was enhanced by the continued growth of the tumor as well as by the radiation. The intense X-ray and radium therapy makes it impossible to judge as to how much of the ossification present in the last microscopic sections was due to this therapy and how much to a more malignant tendency of the tumor. That the ossification is not purely of a reactive nature is shown by the presence of an osteoid matrix in the extensions of the tumor into the soft tissues (Fig. 6).

Case 6. Man, aged 36 years, had noticed for 2½ years increasing pain in the left leg and sacral region; 1½ years, defective sphincter control; ½ year, impotence. Sensory and motor disturbance was present in distribution of the left sciatic nerve. X-ray examination January 3, 1933, revealed focal bone destruction in left half of the sacrum. Operation, January 14, 1933, by Prof. Walzel consisted, first, in the removal of the coccyx and lower segment of the sacrum thus revealing a cocoanut sized tumor on the inner surface of the sacrum, displacing the rectum inward. The tumor was not infiltrative, and possessed a nodular, dark gray capsule. An attempt to mobilize the tumor tore it, thus freeing friable gray masses of tissue. The tumor originated from the sacrum, the inner side of which it completely corroded. Prof. Walzel then curetted the bone and by blunt dissection removed the tumor except for some portions attached to the rectal wall and a portion above the sacral promontory which could not be reached. Pathological report: "Numerous, crumbly, nut sized pieces of cartilaginous tissue with numerous deeply situated cells, the capsules of which were not everywhere well developed. In these areas, the cells lay close together in a strongly basic staining ground substance—chondroma, with transition to chrondrosarcoma."—Prof. Konschegg (Fig. 7). Prof. Sternberg, from the microscopic section alone, regarded this as a chondroma. An X-ray examination 2 months later showed only the operative defect, but 4 months after the operation there was a roentgenologically visible recurrence in the left lateral mass of the sacrum, infiltrated by a number of transparent nut sized areas of irregular contour. Patient was discharged 2 months previous to this time with continuation of X-ray treatment, without pain, and with restoration of sphincter function. Following discharge, the bladder and rectal function was gradually lost. A letter from the patient received 10 months after his discharge told of a huge recurrence and a cachectic condition.

This is a chondrosarcoma very similar to that of the upper femur in structure and course, but the location of which made it inaccessible to complete surgical removal. It is interesting from the standpoint of its chondromatous structure, its corresponding refractiveness to radiation, and its roentgenological translucency, permitting X-ray demonstration only of those parts of the tumor which were destroying bone.

Case 7. A tailor, aged 77 years, gave a history of "gout" in childhood; dislocation of the right hip 20 years before entry. There had been a gradual development of a cocoanut sized tumor on the inner surface of the right thigh during the course of 8 years, which, during a year before the increase in growth began, made its appearance as a very small, allegedly stationary, mass, associated with pain in this region. X-ray report September 22, 1933: "Extensive destruction of the horizontal ramus of the right pubic bone. Extending into the soft tissue from this area is a coarsely granular, flakily calcified tumor the calcium content of which disappears toward the periphery. This under portion can correspond to the rapidly growing sarcomatous part of the tumor. Lungs negative." Radiation was without effect, and the tumor grew until it seemed larger than the rest of the patient. A photograph taken prior to its maximal size development is shown in Figure 8. X-rays before death showed no evidence of osteitis deformans (Paget) in skull, vertebra, pelvis or tibiæ, or tumor formation in these bones or in the lungs apart from the local growth. Autopsy, December 20, 1933: Huge, partly necrotic, partly calcified tumor, occupying most of the right thigh, pelvis, and gluteal region, originating from the right horizontal ramus of the pubic bone, in its peripheral areas of gelatinous character. The pubic bone was the only one destroyed or invaded by the tumor. Histological report: "Tumor tissue crowded

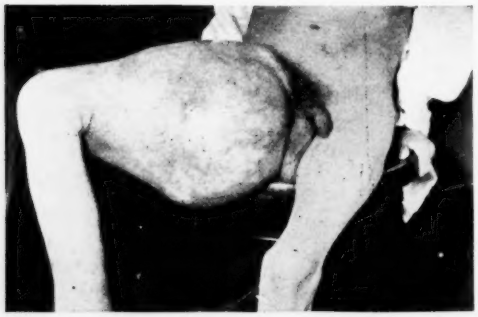


Fig. 8. Photograph just prior to maximum development, Case 7.

with cartilage-like cells, some more, some less differentiated, in places necrotic, in others bearing the structure of an osteoid chondrosarcoma; peripheral portion, myxosarcoma." (Figs. 9, 10, 11.)

The rarity of bone sarcoma after the age of 50 years, and the increasing ratio of bone sarcoma to Paget's disease after this age (4, 12) with the greater frequency of a combination of the two with increasing age, gives note to this case in view of the age of the patient (77 years) and in view of the absence of osteitis deformans. The fact that the patient was a tailor and that the characteristic sitting posture was maintained on and off for over half a century may have been an inciting factor in the tumor growth arising at the origin of the sartorius muscle but it does not call for too serious attention. The apparently uniform growth of the tumor during 8 years is unusual, however; this suggests a primarily chondromatous growth, and taken together with the fact that it was bone destructive only at its point of origin, where the type of resisting tissue was of more consequence in checking a relatively benign growth than an eroding tumor of higher malignancy is significant. It is also worthy of note that, although this sarcoma extended along practically the entire length of the femur, it produced only a mechanical distortion of that bone. The patient described a small tumor at the original site of this growth which disappeared 2 months after the reposition of the disarticulation of the right hip, this accident occurring 11 years before the onset of the main growth. This may have been a hematoma following an anterior dislocation, and suggests the origin of this sarcoma in that type of traumatic osteoma which has been known to follow such a dislocation (27).

CASE 8. Woman, aged 48 years, was struck on left side of chest 5 years previously. Since then this area has been painful and sensitive. Three years before entry there appeared a hard, slowly growing nodule. Three months before admission, a lemon sized tumor and piece of rib were removed in an outlying hospital (report from this operation: "no definite sign of malignancy"). There was recurrence in the operative wound 2 weeks later. Two months after that the growth was excised when it had reached its former size. Histological examination at this time: "osteosarcoma." A week later, there was a recurrence in the wound. Clinic entry: tumor since removal 6 weeks before now grown to orange size. Biopsy: "Tumor consists here and there of thickly distributed cells with a sort of capsule suggestive of cartilage cells. Among these are delicate collagen fibers; occasionally the cells are grown in thicker bands; in other places, there is a predominance of fibers and bone trabeculæ, also mucinous areas with star shaped cells; much necrosis—osteochondromyxosarcoma." X-ray examination demonstrated only a diffusely opaque tumor arising from the wall of the thorax. There was progressive growth of the tumor in spite of intensive radiation. The patient became moribund and was removed from the hospital by relatives.

The location, course, and reported structure of this tumor, with the age of the patient, imply a sarcoma arising on the base of an osteochondroma or chondroma. This is suggested by the initial slow growth of the tumor and the result of the outside pathological examination speaking against malignancy. Whereas the tumor at first required 3 years to reach the size of a lemon, this size was reattained 2 months after the first operation, and less than 6 weeks after the second. Although spontaneous malignant change can lead to a sudden increase in size, this bears the implication that operative interference stood in causal relationship to the further malignant course of the sarcoma. The report of the microscopic section (the slide itself was not preserved), does not, in itself, allow a distinction to be drawn between primary and secondary forms of chondromyxosarcoma.

CASE 9. Woman, aged 43 years, had a hard tumor on the lower gum which she had noticed for 9 months, in which time it had steadily increased in size and several overlying teeth had fallen out. Examination showed a walnut sized, rounded tumor next to the dental margin in the lower anterior alveolar process—smooth, reddish, lobular, containing two loose teeth (Fig. 12—4 wks. after biopsy). Biopsy, April 27, 1934: "Tumor merely surrounds the root of the embedded tooth; covered by stratified epithelium and consists of nests of smaller and larger rounded spindle cells, which are separated by a distinct intercellular substance. Among these cells are scattered giant cells and numerous small islands of cartilage; here and there the tumor invades and destroys the bone" (Fig. 13). X-ray pictures were taken April 28, 1934, and showed: "A bone-containing tumor in the central portion of the lower jaw. Originating from the alveolar border of the incisor teeth, an almond sized tumor shadow consisting of bone tissue and flaky ossification projects forward. The anterior wall of the alveolar process is destroyed in the region of the chin" (Fig. 14). Lungs showed no evidence of tumor metastasis. In the 6 weeks preceding operation and following the biopsy, the tumor had trebled in size. Operation (Prof. Walzel): the

Fig. 9.

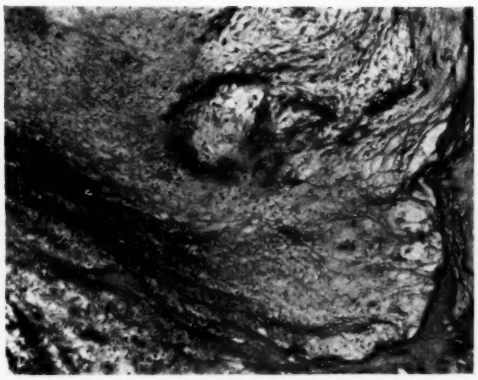


Fig. 10.

Figs. 9, 10, 11. Photomicrographs, Case 7.

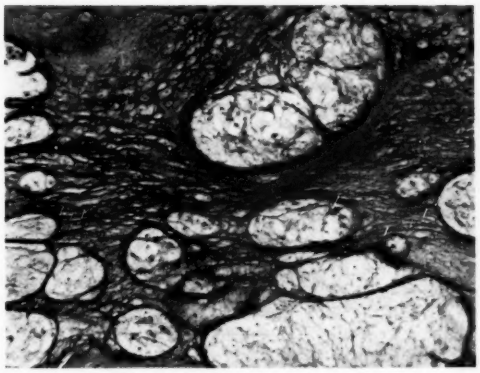


Fig. 11.

tumor, the size of a billiard ball, was removed by chiseling about the broad pedicle arising from the gingival margin; the pedicle was coagulated. Pathological report from operation: "Firm, nodular tumor, glass-like cut surface covered with stratified squamous epithelium, under which are large, round cells, closely placed, also polynuclear cells, as well as small, round, somewhat star shaped cells with jagged, indented nuclei. These cells pass over indistinctly into a pale, blue-staining mass containing cartilage cells lying in large oval capsules; groundwork of delicate connective tissue—chondrosarcoma."—Prof. Konschegg (Fig. 15). Subsequent roentgenogram showed only an operative defect at the previous site of the tumor extending almost to the under edge of the lower jaw without evidence of malignant change in the adjacent bone. Operation was followed by radiation.

The presence of a primary chondrosarcoma is here suggested by (1) the rapid development of this tumor in a short time, (2) the evidently periosteal origin without a preceding chondroma or osteochondroma, (3) the bone formation extending into it at the base and periphery from connective tissue strands which give rise to direct and not to cartilaginous ossification, and (4) the absence of central involvement and presence of myxomatous tissue, although the histological structure in several parts is suggestive of a chondroblastic sarcoma. Its location is unusual, and to the eye raises the question of epulis. This tumor has just been operated on; a cure can hardly be expected. From the type of chondrosarcoma and its location, recurrence will more probably be in the form of lung metastases than at the site of the original growth.

RECAPITULATION

The bone tumors presented here fit into three divisions: enchondroma, and primary and secondary chondromyxosarcoma, according to the criteria given by Geschickter and Copeland. Although they readily fall within the scope of such criteria, they exhibit variations in cartilaginous structure due in part to extensive growth or to treatment. They represent all stages in the evolution of atypical cartilage development: from myxomatous tissue arising from precartilaginous connective tissue, to maturer encapsulated cells lying in a cartilaginous, calcified, or osteoid matrix, or accompanied by direct ossification from strands of embryonic connective tissue. But the predominantly cartilaginous structure allows these tumors to remain securely in the categories in which they are placed, although the occasional patches which show a tendency toward ultimate differentiation substantiate the basis of Kolodny's consideration of all malignant forms of tumors arising from "pre-osteoblastic" cells as osteogenic sarcoma. Enchondromata are only relatively benign; this benignity depends more on their surgical curability than on their histological structure or ulti-

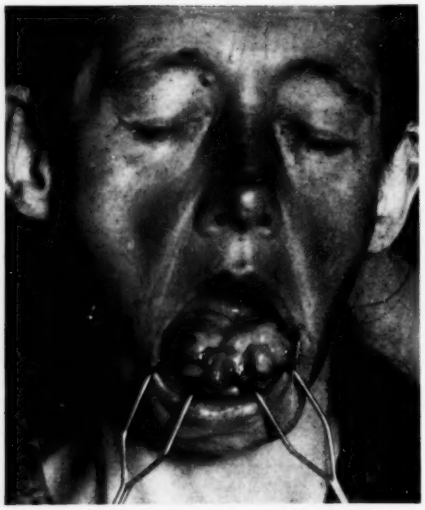


Fig. 12. Tumor protruding from lower jaw, Case 9.

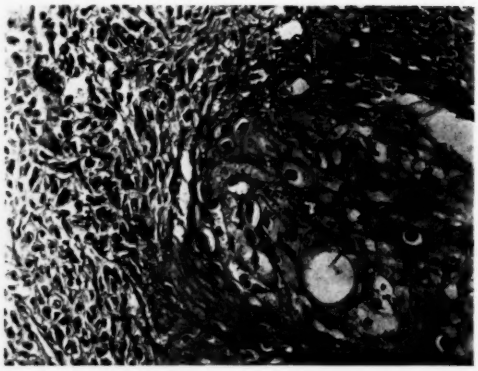


Fig. 13. Photomicrograph, Case 9, biopsy specimen.

mate course when untreated. The great rarity of benign enchondromas of the long shaft bones suggests that the relative stationary nature of those found in the small bones of the extremities is dependent upon something more than the type of constituent cell. That even these may be looked upon with suspicion is justified by the malignant metamorphosis occasionally occurring after many years (20), by the attainment of a tremendous size, and by the occurrence of such cases as that reported by Castren, in which typical small enchondromas of four small bones of the hand were associated with a similar growth in the axillary lymph nodes of the corresponding arm. There are other instances of enchondromas having the pure, unvarying structure of the phalangeal myxoma, but, in a long shaft bone, pursuing a recurrent, metastatic course. The warnings of Bloodgood (5) with regard to the "pure myxoma" of the long shaft bones emphasize the dangerous nature of this type of tissue when it is not confined to the small bones of the extremities, although, as the 9 cases presented here suggest, the predominance of myxomatous tissue is associated with a relatively slow growth and one tending more to local recurrence than to early pulmonary metastasis. One regards with greater complacency the osteomas and osteochondromas containing much bone, and may infer from a comparison of the two that the inhibition and limitation of growth is in great measure dependent upon the bony capsule of the tumor. The stationary character of the central phalangeal chondromas of Case 3, in contrast to the progressive increase in size of the associated cortical chondroma, the fact that a malignant change in an osteochondroma follows operation more often than if operation is not done, and the danger entailed by the spreading of gelatinous myxomatous tissue in an operative wound, contribute further to this belief. The peripheral chondromas of Cases 1 and 3 are the best examples of the restriction; the histological report of the sarcomatous tumor in Case 2 leaves doubt as to the presence of much myxomatous tissue, but varying amounts of this were present in the 6 other cases which ran a less easily controlled course, and in each of these 6 other cases there was no such confinement to a small space by a capsule of cortical bone.

In addition to this factor of confinement by a capsule of cortical bone, a second factor which seems associated with the malignancy of these growths is the greater differentiation of the cartilage cells, contradictory as this statement may seem. The cases in which growth was most rapid and in which there was a tendency toward early recurrence or quick destruction of the adjacent normal bone—those in the jaw, sternum, rib, coccyx, and toe (the last-mentioned an admitted exception)—demonstrate a relatively small amount of myxomatous tissue in contrast to the predominance of islands of highly cellular cartilage, in which the cells are relatively well encapsulated and embedded in a cartilaginous matrix. In these tumors are small areas of calcification, and in some also, areas of bone formed either by direct or by cartilaginous ossification. The opinion that the more highly differentiated cartilage cells grow more in the manner of a malignant growth than in that of less differentiated cells embedded in a

Fig. 14. Roentgenogram, showing destructive process in region of chin, Case 9.

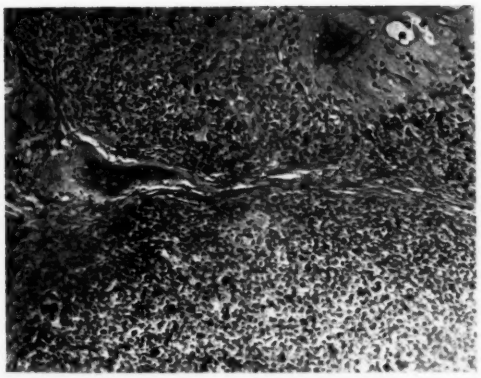


Fig. 15. Photomicrograph, Case 9, from operation specimen.

myxomatous matrix is derived more from the fact that there is a more active corrosion of the surrounding bone and rapid progress than from any reasoning from the standpoint of cell genesis. The best explanation is probably found in the view expressed by Leriche and Policard, namely, that the bony metaplasia in the neighborhood of an area of bone sarcoma results from destruction of normal bone and the liberation of its constituents by the sarcoma, which provide a matrix for the sarcomatous cells. Judged in this light, such differentiation is in reality a measure of the destructive progress of the younger myxomatous tissue rather than a mark of the malignancy of the cells which are surrounded by a cartilaginous or osteoid matrix. It is evident from the two microscopic sections of the chondrosarcoma of the lower jaw (Figs. 13, 15) that a more mature cartilage cell developed during the period of growth acceleration at the expense of the patches of myxomatous tissue which were seen scattered in the material which was removed at an earlier date. Although this need not throw doubt on the more primitive nature of the young cells embedded in the undifferentiated matrix, it does indicate an inhibiting influence of this matrix on the young cells which are embedded in it.

The greater malignancy of the more highly differentiated chondrosarcomas need not conflict with the roentgenological and clinical evidence that large, localized cartilaginous tumors, such as that of the pubic bone in Case 7, containing large, flaky deposits of calcium and osteoid matrix, are more slowly growing and more benign than the infiltrating growths retaining an X-ray translucency. Such calcium deposits, which can be looked upon as secondary to diminished blood supply and necrosis in a slowly growing tumor are to be distinguished from the shadows cast by cartilage and bone which arise through a primary, neoplastic formation of these elements from the cells which are growing malignantly in this type of sarcoma and which are the precursors of the bone and aberrant cartilage formed from them. At the same time, the "malignant differentiation" here referred to is more a property of the individual cells; it never attains the orderly structure of bone trabeculæ and the relation to cartilage found in the roentgenologically more opaque tumors of an osteochondromatous type. Such secondary ossification is the metaplastic accompaniment of a primary cellular malignancy and arises from cells the differentiation of which follows more that of normal bone.

Nevertheless, the impression that myxomatous cartilage is less aggressive than are other maturer cartilage formations in chondrosarcomas is more easily reconciled with the viewpoint that such a gelatinous matrix represents a product of degeneration and not an early embryonic stage. This view is held by most European pathologists, and is reiterated by Prof. Carl Sternberg (36); he regards myxomatous tissue as one of several types of derivatives of embryonic connective tissue which may be present simultaneously with another type of derivative, cartilage, but does not represent an intermediate grade in the formation of the latter. Sections taken from different parts of the huge chondromyxosarcoma of the femur (Figs. 9, 10, 11) suggest that there may be more than one sort of myxoma structure in cartilaginous growths. Circumscribed islands of dark nucleated cells with star shaped cytoplasmic processes embedded in a faintly staining mucinoid

matrix, and seemingly taking origin from bordering strands of early connective tissue, are found in this tumor (Figs. 9, 10); there are also areas of maturer cartilage cells lying in lacunas of varying size and more or less encapsulated; these show, in patches, a transition to a myxomatoid tissue which appears to be associated with a breaking down of these lacunas, and the presence in this mucinous matrix of numerous cells, but in far greater number, of the type enclosed by the lacunas. An extensive microscopic examination of these tumors showed that the myxomatous tissue was invariably more highly cellular than any associated cartilaginous or osteoid growth from which it may seem to have "degenerated." This fact in itself speaks strongly for myxomatous tissue as a precursor, or at least an accompaniment, of other cartilage and osteoid formations and not a product of the latter's degeneration. There were areas in the chondromyxosarcoma of the femur, and in that of the mandible (an example of which is shown in Fig. 13), in which an undifferentiated connective tissue is seen giving rise not only to islands of myxomatous tissue, but at the same time to masses of extremely malignant cells of the chondroblastic type, containing giant cells. This corresponds with the presence of giant cells in the enchondroma shown in Figure 1, and supports the view that all three types of cell arise from precartilaginous connective tissue, and at the same time does not leave out of consideration the possibility that such malignant cells may occur through the metaplasia of this early mucinous cartilage. This is a histological argument in favor of the inhibiting effect of the myxomatous matrix on the cells which it contains. The most striking evidence for the very primitive and undifferentiated character of myxomatous tissue is that advanced by Geschickter and Copeland, who demonstrate it in the earliest development of cells and matrix arising from precartilaginous connective tissue, as well as the structural identity of this tissue with the earliest stages of cartilage formation in the embryo.

A reason for the question of myxomatous tissue as precursor, accompaniment, or degenerative product of cartilage may lie in the differentiation into two types of myxomatous tissue, "generative" and "degenerative," in which the cells of the former represent one of the earliest stages of cartilage development, and those of the latter a higher differentiation of which the incomplete formation of matrix is represented by an accompanying myxomatous matrix, which matrix is the same in the two types, although there is a difference in the cells contained in them. If this is true, a conciliation may be effected by regarding the mucinous matrix of myxomatous tissue as a product, function, or accompaniment of growing cartilage cells, which, depending on the absence or presence of factors permitting its transition to a cartilaginous or osteoid matrix, remains in its juvenile form (generative type) or, in the degenerative type, represents a partial failure of the ground substance of the more mature cells to continue to lay down a cartilaginous matrix through the medium of this basic mucinous substance. Such an explanation still leaves myxomatous matrix characteristic of one of the earliest stages of cartilage development. Whether the type of tissue discussed represents a product of degeneration, or a pure stage of early embryonic cartilage formation, its presence seems to be associated with an inhibition of the invasive, destructive tendency of chondrosarcoma, although apparently only in so far as this ground substance may exert a restricting influence on the cells which are embedded in it.

In addition to confinement by a capsule of cortical bone and the amount of myxomatous tissue present, a third factor is sought in the attempt to differentiate these tumors into primary and secondary chondromyxosarcoma. In this limited group of cases, the classification seemed applicable to six. Only one appeared to be a distinct primary type: the chondrosarcoma of the lower jaw. There is fair evidence that the tumor of the os pubis, and that of the rib, were derived from pre-existing osteochondromas; but those of the sternum, sacrum, and femur are secondary only by inference from (1) location in the skeleton, (2) position in the involved bones, (3) their relative regularity of structure, and (4) predominance of myxomatous tissue or better differentiated cartilage islands. The speed of growth was about the same in the sarcoma of the rib as in that of the jaw, and although this may be attributed in both cases to operative intervention, both were highly malignant, a feature supported by a wild growth of cells in the sarcoma of the jaw, suggesting the typical cells of a chondroblastic sarcoma. In general, this comparison would seem to correspond to the statistics of Geschickter and Copeland, who found 24 per cent of 5 year cures in the secondary form, in contrast to only 5 per cent in the primary form. But when a large series of cases is reviewed, similar variations in malignancy and clinical course are found in both forms, and all types of tissue found in both chondroma and chondrosarcoma may be found in the same growth, so that the preponderance of cell type, and rate of growth of certain types of cell, seem more important than

the tissue which was present at the onset of the malignant course. One is led to the conclusions (1) that secondary chondromyxosarcoma is not more benign in any sense than primary, but that the same type of malignant growth may arise with or without the foundation of a preceding benign lesion; (2) that the presence or absence of this sequence shapes the structural plan, but hardly allows a prediction of the course and outcome; and (3) that the higher percentage of 5 year cures in the group of secondary chondrosarcomas results from the earlier recognition and treatment because of the patient's or surgeon's awareness of the pre-existing growth, and possibly the greater age of the patients in this group.

A fourth factor which seems to add definite growth impetus is an incomplete operation not followed by a radical operation. In 4 cases a marked increase in size seemed to follow an incomplete operation. The chondromyxosarcoma of the upper femur metaphysis, noticed for 3 months, regained its original size 3 months after the initial curettage, and had doubled it 2 months later; after the second local removal, there were two wound recurrences, as well as the attainment of the pre-operative size, within 2 months. This occurred in spite of roentgen and radium therapy which produced the appearance of circumscription and localization of the tumor in the bone at a time when it still continued to spread in the soft parts. The sacral "chondroma," which had caused symptoms for 3 years and at entry was confined to a half of the sacrum, according to the X-ray report, showed an increase in extent 5 months after its partial removal, and the attainment of a fatal size within 10 months from the time of operation. The chondromyxosarcoma of the rib had a history of local pain for 5 years and a small slowly growing tumor for 3 years. Although this may have been an osteochondroma at the outset, it was histologically malignant at least as early as the second operation performed 2 months after the first excision, in which time it had regained its original size. One and a half months after this operation, the size was doubled, and 6 months after the first operation, local infiltration had induced a fatal cachexia. The chondrosarcoma of the lower jaw, grown to walnut size in 9 months, had tripled this size 6 weeks after a biopsy; according to the exactness of measure of time and size, this approaches an 18 fold increase in growth rate following biopsy. These figures may, of course, be enhanced by the fact that malignant tumors grow more by geometrical than by arithmetical progression. Such examples also provide a commentary on biopsies, the advantages of which, in general, however, outweigh the disadvantages (23). This factor of acceleration of growth rate by operation supports the impression, moreover, that the patients with bone sarcoma who are not cured by operation die sooner than those not operated on at all.

A fifth factor in prognosis is to be found in the anatomical location and surgical accessibility of the tumor, which concerns not only isolation in a hand or foot, but a circumscription and limitation of extent which permit a total extirpation. A poorer chance of cure is offered by those chondrosarcomas in the proximity of, or in intimate connection with, compound joint structure—cartilage, synovia, and tendon insertions—especially in the hip and shoulder joints, where complete removal of these structures is difficult. The fact that chondrosarcomas of the proximal portions of the humerus and femur are hardly ever cured may be due, of course, to their being in closer vascular and lymphatic relation to the body than are those more distally located. In spite of the fact that fatal termination following radical operation is not often associated with a local recurrence in the proximal joint structures, the consideration that these structures have a close embryological and developmental relation to the chondrosarcomas leads one to think of a predisposition of the numerous precartilaginous elements in such an area to undergo the same aberrant development as those directly concerned in the formation of the tumor itself. This might occur wherever these elements are in a condition of active metaplasia, as in a growing metaphysis or ossifying sternum, or where a mature but diverse structure lends itself readily to a disturbance of the balance of growth equilibrium. Guleke of Jena has recommended that chondromyxosarcoma occurring in the proximal metaphysis of the femur or humerus be treated not only by enucleation, but by a radical removal, down to the bone itself, of the synovial membranes and articular cartilage of the acetabulum or glenoid. His report that such cases in the upper end of the femur recurred in the neighborhood of the acetabulum as late as 5 to 8 years after radical operation is the reason for this opinion; extension is assumed to have occurred through the tissues of the joint capsule, even though the tumors had not destroyed the cortex of the femur. But the length of the latent period may also be interpreted as the time required for the predisposition of the numerous precartilaginous elements in such an area to reveal itself in further tumor formation, and raises the question whether a chondrosarcoma may not be regarded as a regional affection, and

whether it is to be successfully combated only by destruction or removal of adjacent tissues of which it is essentially a part.

The treatment of the cases presented here will be considered in the light of the factors just discussed. The 2 cases of phalangeal chondromatous growths were treated by amputation; that of chondromyxoma of the finger phalanx remained healed after a year and a half; that it will remain cured is hardly to be doubted. The large tumor of the toe in Case 2 grew rapidly, and in the course of a year had completely destroyed its bone shell. The report of the microscopic section suggests an absence of myxomatous tissue and an irregularity of structure. Four years after operation, the patient could not be traced, but the complete fibrous encapsulation of the tumor within the toe is reasonable assurance that it has not recurred. The postoperative X-ray photograph of the metacarpal chondroma showed bone splinters in the wound bed and an irregularity in the cortex from which the tumor took its origin. From the incomplete curettage of the cortex and the scattering of the fragments in the soft tissue, a recurrence may be expected. This patient was operated on too recently to allow of judgment at present, but a recurrence arising from the same metacarpal bone should justify the removal of the entire bone at the next operation. Such cases are particularly adapted to operative removal. The malignant appearance of the cells from the chrondrosarcoma of the toe was sufficient reason for postoperative radiation, and the effect of this form of therapy in stimulating defensive bone production recommends its application following incomplete removal of a chondroma.

Two cases were too advanced for surgical intervention—the massive sarcoma of the pubic bone, and that apparently originating in a rib and spreading into the thorax. In the former, location and size contributed to a fatal prognosis, and in the latter, the extent and probable presence of metastases.

The chondrosarcoma of the coccyx proved itself at operation to be incompletely accessible, and from its further course, refractive to radiation. The tumor of the body of the sternum seemed to have been totally removed at the first operation, and without an intrusion into the malignant areas which might have freed tumor cells into surrounding tissue. Although it was circumscribed, the tumor contained a variety of cells of cartilaginous origin, progressing to the point of osteoid tissue, and exhibited irregular patches of bone destruction which showed none of the regularity of encapsulation of the chondromatous type. Six months after operation there was a recurrence in the manubrium, which, in its turn, was subsequently removed. The manubrium and body of the sternum are not only parts of the same bone, but cartilaginous ossification is going on at the same time in both, and although the recurrence in the manubrium may have existed microscopically at the time of the first resection, this again speaks for the removal of as much as possible of the genetically related tissue when the situation and extent allow a surgical procedure. If pulmonary metastases do not terminate this case, which at the present time is clinically and roentgenologically free of tumor, a recurrence in the associated costal cartilages is not unlikely (see footnote to Case 4.)

The inefficacy of curettage and radiation in its most direct form—radium implantation—is well illustrated by the case of central myxosarcoma in the upper femur metaphysis. It also shows the outspoken clinical malignancy of a tumor which was of a myxomatous type at the outset, and later on of maturer bone forming cartilaginous tissue. The roentgenograms following X-ray and radium therapy (Figs. 5 b and c) show a striking increase in bone density and a sharp, ossified limitation of the primary tumor area. Though osteoid tissue and bone were present in the malignant cell groups in the surrounding tissue (Fig. 6), this was not enough to be visible in the X-ray pictures, even though this formation may at least have been accelerated by radiation (17). In view of the resistance of such cartilaginous new-growth to X-ray treatment, the benefit derived from this form of therapy seems to rest chiefly on its stimulation of reactive bone formation. Although bone sarcomas of the upper end of the femur are regarded by many as incurable, the acetabular disarticulation performed in this case with the removal of a slowly growing chondrosarcoma in its gross entirety may offer some hope, although the same operation carried out at an earlier date would have proved a better chance of a cure.

The highly malignant primary chondrosarcoma of the lower jaw leaves little room to question that a radical anterior resection of this bone was the most desirable treatment. A bone sarcoma in this location which reached walnut size in 9 months, and trebled this size during 6 weeks following biopsy, does not offer a good prospect of cure by any method. The operation was one of curettage and radiation. The only hope for amelioration by X-ray or radium therapy lies in the extremely rapid growth of the tumor and its undifferentiated chondroblastic cells, which may show a fair degree of roentgen susceptibility.

SUMMARY

1. Nine cases of chondromyxomatous tumors are individually presented and described from a clinical standpoint. Six of these were malignant sarcomas, two chondromas, and one may be regarded as a circumscribed chondrosarcoma occurring in a toe.

2. The close histological relationship of these tumors is reason for seeking a connection between their clinical course and (1) deviations from a unity of structure, and (2) factors apart from their histological composition.

3. From these features are derived factors of prognostic value:

a. Limitation by a capsule of cortical bone, characteristic of the chondromyxomatous tumors of the small bones of the hand and foot, is usually accompanied by a slow, localized growth.

b. A predominantly myxomatous tissue is less invasive and more slowly growing than that in which a greater differentiation of cartilage cells has occurred. Although the standpoint that myxomatous tissue is the least differentiated form of cartilage seems confirmed in these cases, the implied contradiction may be explained by an inhibitory effect of the myxomatous matrix on the cells which are contained in it, and by the view that bony differentiation depends partly on the matrix supplied for its formation by the destruction of bone by the less differentiated cells.

c. The chondromyxosarcomas arising on the basis of a pre-existing osteochondroma or chondroma pursue a less rapid course after the assumption of a malignant character than those which are malignant from the outset. Although this corresponds to the statistics of Geschickter and Copeland, who find a strikingly greater percentage of 5 year cures in the secondary chondromyxosarcomas of their classification than in the primary form, the statistical evidence of the cases presented here is too limited, and much weight cannot be attached to this distinction as a factor in prognosis.

d. An incomplete operation greatly accelerates the growth of a chondrosarcoma.

e. The more proximal location of this type of tumor in a limb, or the existence of such a tumor in bone simultaneously undergoing normal developmental metaplasia or in the neighborhood of numerous structures arising from precartilaginous connective tissue, makes the prognosis less favorable.

4. The method of treatment used in this series of cases is discussed on the basis of the factors governing prognosis. Resistance to radiation, the beneficial effect of which lies chiefly in the stimulation of reactive bone, makes this form of treatment useful only as a supplement to operation. Local, complete removal of an isolated, circumscribed tumor, which exhibits histologically a comparatively uniform structure, makes possible a more radical procedure should there be recurrence. For the outspokenly sarcomatous members of this group, a resection or amputation is advocated; as much as possible should be removed of the adjoining tissues which are composed of cells which exhibit stages in early cartilaginous development related to the tumor itself although of an orderly and normal architecture.

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THE SURGICAL TREATMENT OF SEVERE FORMS OF LYMPHEDEMA (ELEPHANTIASIS) OF THE EXTREMITIES

A Study of End-Results

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SEVERE forms of lymphedema, or elephantiasis, for many years have produced one of the most unsightly, and in many instances one of the most disabling, types of deformity. Particularly prevalent among women, whose cosmetic sense is more highly developed than that of men, it is the source of extreme mental suffering to those afflicted. From milder cases to cases of the most extreme enlargement of the affected part all grades of severity are encountered.

It is not our purpose in this paper to discuss the etiology of the condition. That phase of the question has been covered lately by Allen. Rather we propose to review methods of surgical treatment and to report the end-results from a study of cases in which treatment was given at the Mayo Clinic in the past 10 years. In all these cases a sufficiently long interval has elapsed since operation to be reasonably certain that final results have been obtained.

REVIEW OF LITERATURE

In reviewing the literature on the surgical treatment of any disease one is invariably taken back to the era when this treatment was not based on the principle of correcting or relieving the underlying cause. So it is with the surgical treatment of elephantiasis. The earliest method of treatment probably was that of scarification, proposed by Lisfranc in the first half of the nineteenth century. Later, Carnochan (1851) ligated either the external iliac or femoral artery with the view of restricting the circulation and thus of decreasing edema. Improvement did not result and gangrene often followed. In the early part of the twentieth century, Dieffenbach, Mikulicz and others excised portions of affected skin and subcutaneous tissue; some temporary improvement followed, although it was questioned whether this was due to rest in bed or to the result of operation.

It was not long after reports of Dieffenbach's and Mikulicz' work appeared in the literature that surgical treatment of lymphedema assumed an entirely different aspect. This, no doubt, had its origin in the discovery that the edema was due primarily to lymphostasis. Since the time that this knowledge was acquired, all surgical procedures have striven to provide a means of reestablishing the lymph flow or drainage. To Handley goes the credit for leading the way in this field; in 1908 he proposed a method of draining the obstructed regions into adjoining healthy tissues. He attempted to accomplish his purpose by inserting 4 long silk threads in subcutaneous tissue, the threads extending from the ankle to the deeper tissues of the abdominal wall. Later, Lexer modified the method by substituting strips of fascia for the silk threads; the results generally were unfavorable. However, more recently, Keysser, after trying several methods reported the best results from a combination of Lexer's and Handley's methods. Lefebvre (1926) has reported 26 cases in which patients were treated by this method with rather unsatisfactory results. Several years after Handley's work appeared, Walther further modified the method by burying a rubber tube between the deep fascia and the layer of muscle; the tube extended from the lower portion of the thigh to the lower portion of the abdomen. The lower end of the tube was left protruding through the deep fascia into the edematous tissue and the upper end was similarly placed in normal tissue. Following the operation, the extremity was elevated and bandaged. Ten cases were reported in which the results were satisfactory after a short time had elapsed. There were no later follow-up studies.

At the same time that Handley was trying to establish new lymph channels by the production of a reaction around a foreign material, others were approaching the situation from another angle. They were attempting to establish channels between deep and superficial tissues. Since deep fascia is not permeated by lymph channels, all procedures had to be directed either toward removing the fascia or making openings through it. Lanz was the first to devise a means of communication between superficial and deep tissues.

He made a longitudinal incision throughout the length of the thigh on the lateral surface. The incision extended downward through the fascia lata and intermuscular septum to the bone. The bone was then trephined and the marrow cavity opened in 3 places. Pedicled strips of fascia lata were then cut and inserted into the holes and attached to the openings in the marrow cavity. He hoped to establish drainage from the superficial tissues into the muscles and bones. In addition, he made slits in the deep fascia. Lanz' procedure was quite complicated, and the followers of his method dispensed with trephining the bone because it had no added advantage. Oppel was the first to make such modifications. He turned strips of fascia and edematous subcutaneous tissue in between the muscular layers and sutured them there. Furthermore, he extended the operation to the leg. Rosanow followed this same procedure, except that he turned triangular flaps in between muscular layers.

Kondoleon, about the same time and working on the same principle as Lanz, devised a simpler procedure which would accomplish the same end-result. He made a longitudinal incision the entire length of the extremity on both the lateral and medial aspects. The fascia was incised and its edges were sutured into the intermuscular septum. He later modified the operation by excising a strip of edematous tissue and fascia, about 5 centimeters wide, from the entire length of the incision. The skin was allowed to drop down in contact with the muscles and the incision was closed without drainage. Six patients were treated by this method with good results. Still later, however, Kondoleon reported that the results were not so satisfactory as he had hoped, but that they were encouraging enough to justify operation in cases of marked lymphedema and elephantiasis. Kondoleon's technique was based on some experimental work in which he had shown that a broad communication must be established between the subcutaneous and muscular layer by removing the fascia which prevented such communication. If this was not done, one could not hope to clear the edema. The year following Kondoleon's description of his operative method, Matas made the most complete survey of the literature to be found, and he reported 2 cases in which patients were treated by this method with satisfactory results. Later, Burke reported 16 cases in which patients were treated by the Kondoleon method; of these, end-results were given in 12 cases. Six patients were definitely improved, the condition of 2 remained unchanged, and 4 were definitely worse.

Since Kondoleon first devised the operation, several modifications in the technique have been made, but the general principle of the procedure has remained unchanged. Each successive modification has attempted to establish a broader communication between the deep and superficial tissues. Of all the various modifications, Sistrunk's has been followed by the most uniformly satisfactory results. He stressed pre-operative preparation, and this consisted essentially of rest in bed, with the extremity bandaged and elevated for 10 days to several weeks. After the patient had been properly prepared, the operation was carried out in 2 stages; one side of the extremity was operated throughout its entire length at the first stage and, 2 to 3 weeks later, the other side was operated. At the first operation an elliptical incision was made from the iliac crest to the ankle on the lateral surface and, at the second operation, from the groin to the ankle on the medial surface, a sufficiently large piece of skin being removed to reduce the size of the extremity to almost normal. The margins of skin were then dissected back for a distance of 6 centimeters on each side, and edematous tissue incised downward through the deep fascia at this point. The skin, edematous tissue, and deep fascia down to the muscle were then removed in one piece. This allowed a broad communication between superficial tissues and underlying muscles. The skin was closed without drainage and a snug fitting bandage applied. Immediately following the operation, isotonic salt solution was given by rectum and subcutaneously. Morphine and epinephrine also were given as a further preventive of shock. Sistrunk's post-operative treatment consisted of the wearing of an elastic stocking or rubber bandage for an indefinite period of time. After about a year's time, an attempt could be made to discard the bandage, but if swelling tended to recur, the bandage was re-applied and worn until such a time as it could be discarded without any resultant swelling of the extremity. If the swelling tended to recur even when the bandage was worn, the patient was placed in bed for a few days at intervals when the conditon required it. In cases in which this regimen was followed, the results usually were favorable. Sistrunk reported 40 cases in which patients were treated by this method; 30 of these patients obtained good results and 10 were unimproved.

Several other modifications of the Kondoleon technique have been made, but all of these essentially were the same except that of Kimura. He performed the operation as prescribed by Kondoleon but, in addition, removed a long flap of

diseased skin and subcutaneous tissue close to its juncture with healthy tissue. He then turned down a pedicled flap of good skin and sutured it in the site where the diseased skin had been removed. Nine patients with involvement of the lower extremities were treated by this method with good results. More recently Professor De Gaetano suggested some modifications in the operation; however, these were similar to Sistrunk's except that De Gaetano did not remove as broad a strip of skin and fascia. Good results were reported. Battista has reported 2 cases in which treatment was by this method, and in both, results were good. Auchincloss made modifications in the Kondoleon technique which probably were a little more extensive than Sistrunk's. By his procedure all of the fascia surrounding the extremity could be removed by the 2 stage procedure. End-results were not given in this report. Later, Torgerson reported 5 cases in which patients were treated by this method. The results were good at the end of 6 months. Del Toro and Pons reported 12 cases of patients treated by this method; of these, 6 patients obtained fair results, 4 were not improved, and 2 were not followed.

Recently, Knutzen made a very extensive review of the foreign literature on the subject and discussed various types of operation. Sixteen cases in which operation had been performed were reported; of the patients, 2 obtained complete relief, 6 were greatly improved, 4 were slightly improved, and 3 received no benefit.

SELECTION OF CASES

The selection of cases for operative treatment is one of the most important factors leading to the success or failure of the operation. Severe cases of lymphedema of either extremity are all, of course, fit cases for operation, provided contra-indications are not found on general examination. Recurrent attacks of cellulitis do not constitute a contra-indication to operation, although, of course, operation should be performed at times as far removed from the time of such attacks as possible. Patients with milder degrees of lymphedema in general are not good subjects for surgical treatment. In these cases the condition can be improved, but in most instances improvement is not as great as the patient expects and disappointment results. Many of these patients will need surgical attention later, however, unless a great deal of care is used in the wearing of the bandage. The patient should be warned that some form of supporting bandage or stocking must be worn after operation for an indefinite period.

PRE-OPERATIVE TREATMENT

Pre-operative treatment similar to that described by Sistrunk is prescribed. However, in our recent cases we have elevated the leg in a specially built sling (Fig. 1). This sling is elevated so that the leg rests at an angle of 75 degrees from the horizontal plane of the patient's body when lying in bed. This elevation, together with bandaging and, if necessary, massage, is used without interruption, and the patient is not allowed out of bed. In this way edema may be greatly reduced in a few days, usually in not more than a week, and we are then able to proceed with the operation. The edema should be reduced before operation is attempted if a good result is to be obtained. The time required to clear edema will vary from 2 to 3 days in mild cases to a week or 10 days in very severe cases.

Under the routine of rest and elevation, any infection or ulceration which may be present will clear very rapidly. In any case, all superficial and deep infections should be cleared completely before operation.

In cases in which cellulitis has been a serious complication, and particularly in those cases in which rest does not reduce this infection promptly, much can be accomplished by immunization with antistreptococcic vaccines until the resting infection has subsided.

OPERATION

The operative technique we now use is essentially the same as Sistrunk's, with the exception that we follow the modifications that were proposed by Walters. These modifications are: (1) the use of spinal anesthesia, (2) the use of a tourniquet, (3) the use of supportive treatments at the time of operation, and (4) allowing a longer interval to elapse between the 2 stages of operation, usually from 3 to 6 months. With the patient under spinal anesthesia, the entire extremity and lower portion of the trunk is prepared surgically. A tourniquet is applied as high up on the extremity as possible. The operation is carried out on the outer side of the extremity in the first stage. Two elliptical incisions are made throughout the entire length of the extremity and up to the iliac crest on the outer side. These incisions are about 8 centimeters apart at their widest separation and connect at each end. The flaps of skin are dissected back until nearly half of the circumference of the extremity is exposed. The edematous tissue and deep fascia are then incised down to the muscle layer. The subcutaneous tissue and deep fascia along with the skin are then removed in one piece leaving the broad region of muscle

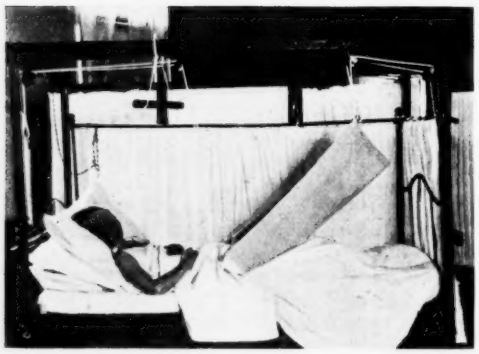

Fig. 1. Leg elevated in sling.

TABLE I.—RELATION OF SEVERITY OF ELEPHANITASIS TO IMPROVEMENT

	Patients							
	Improvement, grade					Died*	Results undetermined	Total
Severity	0	1	2	3	4			
Mild	1	1		3			1	6
Moderate	4	4	4	10	5	2	3	32
Marked	3	4	1	7	2	3	4	24
Extreme						1	1	2
Total	8	9	5	20	7	6	9	64
Per Cent	12.5	14.1	7.8	31.3	10.9	9.3	14.1	100

*Died from operative shock, 3; from erysipelas, 2 years after operation, 1; from embolus, 2 years after operation, 1; and from an unrelated condition (lymphosarcoma), 1.

bare. When the margins of skin are brought together, the skin comes in direct contact with this large surface of muscle, allowing a broad communication between these structures. The operation has been carried out so far in a dry field with the aid of the tourniquet, but the tourniquet is now released momentarily to allow ligation of any bleeding points, and is then reapplied. The wound is then closed without any drainage. The tourniquet is again released for a moment and then reapplied. This procedure is repeated for several minutes, thus slowly restoring the circulation of the extremity. We believe that this slow return of the circulation in the extremity is a big factor in preventing postoperative shock. The extremity is then bandaged snugly and the patient is returned to bed. The extremity is not elevated, and the head of the bed is not lowered. Five hundred cubic centimeters of 6 per cent of acacia in physiologic saline solution are given intravenously. Morphine sulphate, or some other sedative, is given for pain. Since the institution of this technique, as herein described, the incidence of shock has been very low and no operative deaths have occurred.

POSTOPERATIVE TREATMENT

The dressing is changed at the end of 10 days and, if the wound is dry and healed, the stitches are removed. The patient is allowed to get out of bed at the end of 2 weeks if no complications have occurred. However, before the extremity is placed in the dependent position, a snugly fitting elastic stocking or a para-rubber bandage is applied over its entire length. This support is worn for at least 1 year and until such a time thereafter as it may be discarded without return of the edema. If edema returns following operation, even though the bandage is worn constantly, the patient is placed in bed for a few days until it subsides. When this routine is adhered to closely by the patient, a good result will usually be obtained. However, in a few of the severe cases, regions of thickened skin may have to be removed at some later date.

TABLE II.—RELATION OF WEARING OF BANDAGE TO IMPROVEMENT

	Patients									
	Died*	Improvement, graded					Little or no improvement Total		Improved Total	
		0	1	2	3	4	Number	Per cent	Number	Per cent
Wearing bandage	3	5	6	5	18	6	14	27.5	29	72.5
Wearing bandage questionable		1	2		1		3	75.0	1	25.0
Not wearing bandage†		2	1		1	1	3	60.0	2	40.0
Total	3	8	9	5	20	7	20	34.7	32	65.3

*All 3 died 2 years after operation.
†One of these patients had only very mild elephantiasis of the feet and ankles.

Fig. 2. Left, Before last operation and, right, after last operation.

Fig. 3. Left, Pre-operative and, right, postoperative appearance.

CASES STUDIED

Sixty-four patients have been operated on at the Mayo Clinic by the modified Kondoleon method since Sistrunk's report of his technique in 1923. In this study we have followed these cases over a period of from 2 to 10 years. Of the 64 cases, end-results were learned in 55. In compiling these results, the information was secured by 2 methods, namely, by personal examination of the patient and by letters of inquiry after a sufficiently long period had elapsed following operation to determine the final result. It must be remembered, however, that data obtained by letter are not as reliable as those obtained by personal examination; in many cases, however, one has to depend on these data because of the inability of the patient to return for an examination. There is also a group of patients from whom one cannot get information by letter. Nine of our patients were in this group.

The improvement among patients whose cases were followed was graded on a basis of 0 to 4, the latter signifying almost complete relief (Table I; Figs. 2, 3, and 4). According to this grading, the condition of 12.5 per cent of the patients was unimproved; that of 14 per cent was improved, Grade 1; that of 7.8 per cent was improved, Grade 2; that of 31.3 per cent was improved, Grade 3, and that of 10.9 per cent was improved, Grade 4. A mortality rate, both immediate and remote, of 9.3 per cent was noted. The 3 postoperative deaths made an operative mortality of 4.7 per cent. Further analysis of the cases revealed that there was very slight relationship between the severity of the disease and the degree of improvement.

A satisfactory degree of improvement was noted in 42.2 per cent of the cases, whereas in 21.8 per cent there was some improvement, although not enough to be called very satisfactory. These results were influenced by the wearing of an elastic supporting stocking of some sort. We have

Fig. 4. Left, Before last operation and, right, after last operation.

TABLE III.—RELATIVE INCIDENCE OF INFECTION BEFORE AND AFTER OPERATION

Infection	Patients						
	Before operation	After operation					
		Died	State of infection				
			Undetermined	More severe	Unchanged	Improved	Cleared
Phlebitis	6	1*	1	‡		1	3
Cellulitis	15		¤		3	5	7
Erysipelas	4	1†				2	1
Eczema	1					1	
Total	26	2	1		3	9	11

*Died from embolus 2 years after operation.
†Died 2 years after operation.
‡A small ulcer developed in 1 case in which the patient had not suffered from infection before the operation.

already stated that some form of supporting bandage must be worn after operation. Thus, it is seen (Table II) that real improvement was found in 72.5 per cent of those cases in which the patients were known to be wearing a bandage after operation, whereas in only 40 per cent of those cases in which a bandage was not worn was the condition improved.

The relative incidence of infection before and after operation showed marked improvement. Of 26 cases in which the patients were suffering from recurrent attacks of infection of some sort, in only 6 was the infection worse or unchanged, whereas in 9 it was much improved, and in 11 it had completely disappeared (Table III).

COMMENT

Practically every one of the succeeding modifications of the original Kondoleon operation has been accompanied by some improvement in the results obtained. The principle of the operation, however, has remained unchanged, namely, of establishing a communication between the deep or muscle layer and the subcutaneous layer. The conception that this procedure resulted in a communication between the superficial and deep lymphatic systems has been discarded, and it is now thought that the superficial lymph vessels drain directly into the vascular network of the muscles. Each of the succeeding modifications has striven to increase the communication between these 2 regions.

Sistrunk made the greatest advance in accomplishing this end when he removed a much wider strip of edematous tissue and fascia as well as a strip of skin. This modification was followed by much improvement in the results. All other changes have added very little to the extensiveness of the operation. Additional modifications have been made in Sistrunk's technique which have simplified the operation from the standpoint of severity and led to more satisfactory results. Adequate preparation is very important because, if edema is not controlled prior to operation, the procedure is much more difficult, the fascia usually is not so extensively resected, and the results are not as good. For this reason we stress rest in bed until edema has completely subsided.

The use of the tourniquet has proved very valuable in our cases. Bertwistle and Gregg, on the other hand, found the tourniquet to be of no value. Its failure in their cases was probably due to insufficient pre-operative preparation, that is, the edema of the extremity had not been controlled. Torgerson did find the tourniquet very valuable. Since we began to use the tourniquet the incidence of shock has been reduced to a very small percentage and no operative deaths have occurred. It must be remembered that the slow release of this tourniquet over a period of several minutes is also a big factor in the prevention of operative shock.

In the postoperative care of these patients, many failures to obtain a good result are due to the patient's neglect in wearing a support. Often the problem arises of sufficiently impressing these patients with the necessity for wearing the bandage. If one is patient enough, however, this point can be impressed on almost all of them; it must be done if a satisfactory result is to be expected. If the bandage is worn continuously when patients are on their feet, the results are usually favorable. Occasionally the swelling will tend to return for some time after operation; in such cases a few days' rest in bed will control it.

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THE CORRECTION OF HIP FLEXION DEFORMITY IN ANTERIOR POLIOMYELITIS

A Result Study

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THIS study is based on hip flexion deformities in 130 children treated at the Shriners' Hospital for Crippled Children at Springfield, Massachusetts, from its opening in February, 1925 to November 1, 1933.

We agree with previous authors that this condition is one of the most disabling distortions complicating infantile paralysis (1). Even a mild degree of deformity contributes markedly to the limp and functional disability, while a deformity of more than 30 degrees produces a distressing exaggeration of the lumbar lordosis. More extreme deformity may be sufficiently crippling to prevent walking, and to limit the unfortunate individual to a wheel chair existence.

In common with other paralytic deformities, hip flexion, which is commonly a combination of flexion and abduction, is produced by imbalance of antagonistic muscles with adaptive shortening of the relatively stronger muscles. The deformity is further aided and abetted by habitual flexion in sitting and in recumbency. The characteristic inherent property of muscle tissue to contract when insufficiently opposed produces a structural shortening of the hip flexors; namely the tensor fascia femoris, sartorius, rectus femoris, anterior portion of the gluteus medius and minimus, and the iliopsoas. These are enumerated in what appears to us to be their relative importance in producing the deformity. Occasionally there may be changes in the capsule of the hip joint preventing correction, but we have not met any such cases.

We have included in this series, 9 children with paralysis due to lesions of the spinal cord, since the nature of the deformity is the same as in poliomyelitis. Six of these were due to spina bifida, 2 being complicated by large sacral meningoceles. The others were due to birth trauma. Eight of these cases were bilateral making a total of 17 deformities. The meningoceles were also repaired.

INCIDENCE

The incidence of hip flexion deformity as occurring at this clinic is shown by the fact that during this same period 622 cases of infantile paralysis were admitted. The deformity was found in approximately 19 per cent or 1 of every 5 cases.

The deformity was seen more often in boys than in girls with a sex ratio of 82 boys to 48 girls, or 63 per cent males to 37 per cent females. There were 38 bilateral cases equally divided, with 19 males and 19 females. Consequently, the total 168 deformities were 101 boys, or 60 per cent, and 67 girls, or 40 per cent.

In 64 cases, or approximately 38 per cent, the correction of hip flexion was the only surgical procedure undertaken at the time of operation. In the 104 remaining corrections, or 62 per cent, some other concomitant surgical procedure was carried out.

The deformity may occur at any age throughout childhood, being seen in these cases as early as 2 months, and in 10 instances under 3 years. From the age of 3 to 15 the incidence was fairly constant with about 10 cases in each year period, with slightly greater incidence between the ages of 5 and 10 years.

The deformity may also occur very early after the onset of paralysis unless particular precaution is taken to recognize the danger and prevent it by proper splinting and physiotherapy. In this series one patient developed a deformity of 30 degrees in only 4 months. In about one-half of the cases paralysis had been present from 3 to 5 years with approximately 20 per cent less than 3 years and 30 per cent more than 5. From 6 to 14 the distribution was practically the same for each year. Within limits, the deformity tends to be proportional to the duration of paralysis and is progressive to a certain extent. The most marked deformities, however, in this group were from 8 to 10 years' duration.

The amount of deformity when recorded in degrees varied from 10 to 90 degrees and averaged about 40 degrees. An extreme deformity, that is 60 degrees or more, was present in 20, or 19 per cent of the numerically recorded cases. This is somewhat less than Speed reported in his series in which he found a deformity of 60 degrees or more in 24, or 34 per cent, of 70 cases under 15 years of age. A moderate deformity (30 to 60 degrees) was present in 69 cases, or 61 per cent; while 24 cases, or 20 per cent, showed a mild deformity of less than 30 degrees.

CORRECTIVE PROCEDURES

Five methods of correction of the deformity were used in these cases, namely (1) stretching alone, (2) subcutaneous tenotomy of the structures at the anterior iliac spine, (3) subcutaneous tenotomy of the iliotibial band above the knee, (4) open division of the iliotibial band, and (5) fasciotomy of the hip. These methods were combined in varying ways making a total of eight groups of procedures. In addition to the five listed, (6) a subcutaneous division of the iliotibial band was combined with a fasciotomy of the hip and (7) open division of this structure was combined with subcutaneous fasciotomy at the hip or (8) with open fasciotomy. Each of these groups will be considered individually, with the results and analysis of failures in those cases which have been observed for a minimum of 1 year.

STANDARD OF ESTIMATING RESULT

The result in each case has been classified as either good or poor. A good result was considered to be a case in which complete extension in both abduction and adduction has been maintained for at least 1 year. The selection of this time limit is arbitrary, since only 33 per cent of the recurrences have occurred during the first year, 33 per cent occurring during the second year, while one-third have appeared as late as 4 to 6½ years after correction. However, the exclusion of the 18 cases followed less than 1 year eliminates no failures, while 10 of the total 30 poor results are among the 39 cases followed between 1 and 2 years. Consequently, the arbitrary minimum of 1 year was imposed. With selection of corrective procedure there have been no difficulties encountered in obtaining complete over correction in all cases. There has been no operative mortality and no complications. We believe this to be due in part at least to gradual postoperative stretching rather than immediate fixation. The chief problem is in maintaining rather than obtaining correction.

STRETCHING

Simple stretching was used alone in 2 cases. Both were girls with mild deformity, slight in one and 15 degrees in the other. The first (W. G. 530) was 10 years old and had had paralysis for 1 year. She was hyperextended for 4 weeks. Four years later, however, she returned with a deformity of 35 to 40 degrees, requiring operation. The other patient (N. B. 619) has maintained her correction for 2 years. She was 6 years old and had had paralysis for 4 years when corrected. The fact that this method of correction has been attempted in only 2 instances indicates our agreement with the general opinion that stretching methods are ineffective. Even with favorable selection, the results are only 50 per cent satisfactory.

Postoperative stretching, however, is a very important part in the care of these cases, and this has been carried out for a varying period in all cases. A long leg plaster is applied to the affected leg and, as soon as the postoperative reaction is over, the hip is gradually hyperextended by dropping the leg through an elevated Bradford frame from which the lower canvas has been removed. The pelvis is controlled by a plaster jacket or by flexion of the good hip in unilateral cases.

TENOTOMY AT THE ILIAC SPINE

Subcutaneous tenotomy of the structures attached to the anterior superior iliac spine was done alone in only 3 cases, indicating our agreement with Steindler and others that such procedures are generally insufficient. In one case (V. B. 1373), a girl of 10 years, with paralysis for 4 years, showed only a mild deformity which was originally corrected by open division of the iliotibial band and subcutaneous tenotomy at the hip. After 1 month of postoperative stretching, there was still a deforming band present which was divided. However, the procedure was still unsatisfactory as the deformity recurred after 1 year. The other two hips were associated with dislocation in a 4 year old boy (R. H. 2248) with spina bifida. Tenotomy was done preliminary to closed reduction, and the child has been followed for less than a year since the correction.

TENOTOMY OF THE ILIOTIBIAL BAND

Subcutaneous division of the iliotibial band was done twice alone, and three times combined with an open fasciotomy of the hip. The first two were in young boys (R. S. 498 and W. MacD. 979), aged 4 and 2, with paralysis of 3 and 1½ years' duration. Correction has been maintained for 6 and 4 years since operation. The other cases (K. W. 1598 and V. DeB. 2015) were 7 and 10, with paralysis of 4 and 5 years. The deformities were 40 degrees. Correction has been maintained 2 and 1 years. In spite of these results, we feel that the procedure is rarely to be recommended, as it is difficult if not impossible to divide the deep intermuscular septum completely without adequate exposure.

OPEN DIVISION OF THE ILIOTIBIAL BAND

Open division of the iliotibial band was done alone 40 times in 34 children. The procedure used was that described by Yount in 1923. The lower

part of the iliotibial band is exposed immediately above the knee joint and divided transversely. The extension deep in the intermuscular septum is completely divided and the periosteal attachment to the femur reflected upward. The wound is then closed with subcutaneous and skin suture. During the procedure the leg is held in adduction and maximum extension which makes the deforming band stand out prominently. The operation is simple, short, and can be done under novocain infiltration if desired.

The age of the patients having this procedure alone varied from 15 months to 15 years, with two major groups of about one-third each from 6 to 8, and 13 to 15, inclusive. The duration of paralysis varied from 4 months to 14 years with most of the cases from 1 to 5 years. In the 23 measured deformities, the angle of deformity varied from 10 to 70 degrees, with 30 per cent of the cases under 30 degrees, 57 per cent from 30 to 60, and 13 per cent 60 or over.

There are available for follow-up study 31 cases with 35 operations, which have been observed over a period of from 1 to 8 years. Nine have been examined one year after operation; 8, two years after; 6, three; 4, four; 2, five; 1, six; 4, seven; and 1, eight.

The following 5 cases (14 per cent) have shown a recurrence of deformity.

CASE 1. A girl, of 8 years (D. P. 1056), had had paralysis for 5 years. The deformity was bilateral and amounted to 20 degrees on the right and 40 degrees on the left. The extensors were absent; the flexors good. The right leg had an open division of the iliotibial band alone, while the left in addition had a subcutaneous tenotomy of the structures attached to the anterior superior iliac spine. Hyperextension was difficult to obtain and she was stretched for 8 weeks after operation. The paralysis was very extensive, but the child was made ambulatory with bilateral caliper braces and crutches. She walked very little, however, and 3 months after operation beginning recurrence was noted. Two years after operation the deformity amounted to 30 degrees on the right and 45 degrees on the left. She was then readmitted and the deformities were again corrected by a hip fasciotomy on the left and combined fasciotomy and division of the iliotibial band on the right. She was again hyperextended for 8 weeks, but 6 months later the deformity had again recurred bilaterally. The important factor in the failure in this case was the lack of co-operation of the patient and her parents, who seemed satisfied to permit a wheel chair existence, in spite of their protestations to the contrary.

CASE 2. An infant corrected at 15 months of age (I. W. 412) had had paralysis for 13 months and presented 40 degrees of deformity. The extensors were absent, the flexors fair. She was lost from observation for a considerable period, but at the age of 6, 5 years after the correction, she was found to have 20 degrees of hip flexion deformity.

CASE 3. A 3 year old boy (A. P. 133) had had paralysis since the age of 3 months. At time of operation he presented 20 degrees of deformity. The extensors and flexors were both rated as fair. He maintained his correction for a considerable period but at the age of 9, 6½ years after operation, he was found to have a deformity of between 20 and 30 degrees.

CASE 4. A girl of 2½ years (E. B. 782) had had an acute attack at the age of 6 months. She had a deformity of 35 degrees at the time of operation. The extensors were rated as poor, while the flexors were fair plus. She maintained her correction for 4 years when a recurrence of 15 degrees was noted on examination. This was corrected by a combined fasciotomy and division of the iliotibial band and correction has been maintained for 1 year.

CASE 5. A 5 year old boy (J. P. 1708) with paralysis for 3 years had a bilateral deformity. The extensors were totally paralyzed, the flexors were poor. He has been observed for 2 years and while the right is still completely corrected, the left hip shows a very slight recurrence.

Two other cases in this group are of particular interest as they represent failures of previous correction. The first is a girl (W. G. 530) of 14 years with paralysis of 5 years' duration, and bilateral deformity. Four years previously her deformity had been corrected in this clinic by stretching. The other case, also a girl (E. F. 424), was 15 years old with paralysis of 10 years' standing and slight bilateral deformity. The extensors were poor and the flexors absent. Eight years previously she had bilateral correction apparently by Soutter fasciotomies at the Boston Children's Hospital. She has maintained her correction for 7 years since her second operation.

HIP FASCIOTOMY

Fasciotomy of the hip was done 45 times on 37 children. The procedure employed is a modification of Soutter's method which he presented in 1914 (2). The anterior superior iliac spine is exposed through an oblique incision 2 to 3 inches long extending from immediately below the spine obliquely toward the trochanter. The spine is denuded and the attachments reflected down as far as the anterior inferior spine. The contracted fascia over the tensor fascia femoris is divided transversely, and the wound closed with subcutaneous and skin sutures.

The age of these patients is somewhat greater than where the iliotibial band alone was divided, varying from 1 to 15 years with about one-half 10 years old or over; the duration is slightly longer, varying from 1 to 14 years with about one-half 6 years or more; and the deformity is a little more severe, varying from 20 to 80 degrees with half the cases showing 45 degrees or more deformity. Thirty-five cases with 41 operations are available for follow up having been observed from 1 to 7 years. The period of observation was 12 cases for 1 year, 12 for 2 years, 5 for 5, 8 for 6, and 4 for 7 years. Nine cases, or 22 per cent, showed recurrence of deformity. This may be compared

with Steindler's (2) report of his results in 75 cases of hip flexion corrected by the Soutter method observed over 1 year. Using the same standard as that on which we insist, namely, complete extension in abduction and adduction, he found good results in 66 cases, or 88 per cent, and poor results in 9 cases, or 12 per cent. Speed, in a series of 120 operations by Campbell's technique, obtained 83 per cent good results.

The 9 failures include 7 single cases and 1 bilateral. These were 3 girls and 6 boys.

CASE 1. D. P. 1056 has been cited under open division of the iliotibial band.

CASE 2. A boy (F. C. 419) aged 9 years at the time of operation, had had paralysis for 7 years and presented a deformity of 30 degrees. Muscle test showed extensors poor, flexors normal. Four years after operation a slight contracture in abduction was noted. The slight amount of shortening which was present, however, compensated the abduction, so that it was not functionally disturbing. During 3 more years of observation the deformity has not increased.

CASE 3. A boy (S. T. 244) aged 7 years had a paralysis of 5½ years' duration and a deformity of 20 degrees. Muscle test showed extensors fair, flexors normal. One year after operation a recurrence of 15 degrees was observed, which increased to 20 degrees and was corrected by a second fasciotomy 4 years later. Correction has been maintained for 1 year following the second operation. This child also presented a recurring knee flexion deformity more severe both functionally and anatomically than the hip deformity, which was also corrected at both admissions.

CASE 4. A boy (R. D. 974) aged 11 years with paralysis due to spinal cord injury at birth with hip flexion deformity of 60 degrees on the right and 65 degrees on the left. One year and 9 months after operative correction a deformity of 30 degrees was noted at the right hip, the left still being fully correctible.

CASES 5 and 6. An 11 year old girl (V. B. 1373) had a paralysis of 5 years' duration, with bilateral deformity. One year previous to this operation she was admitted for a similar deformity of 40 degrees at each hip. Correction was attempted on both sides by open division of the iliotibial band and subcutaneous tenotomy at the anterior superior iliac spine. Postoperative stretching was continued for 4 weeks, when a tight band which prevented hyperextension on the left was divided by a subcutaneous fasciotomy at the hip. Six months later a recurrence of deformity at the right hip was first observed, and in 2 months more this was noted on the left. One year after the first correction the deformity amounted to 40 degrees on the right and 20 degrees on the left. Open fasciotomies were done and the deformities again corrected. Three months later 30 degrees of flexion deformity was again found to be present and this has persisted for 2 years.

CASE 7. A boy (E. C. 668) of 7 years, with paralysis for 3 years, was corrected by a hip fasciotomy. Hyperextension was present for 4 months but 1 year later 30 degrees of flexon deformity had recurred. Eighteen months after the first operative correction, the procedure was repeated. This correction has been maintained for 1 year.

CASE 8. A boy (R. B. 2080) of 6 years with acute onset of paralysis 5 years before, presented a deformity of 50 degrees. Extensors rated fair minus and flexors fair plus. Correction was obtained and the hip stretched in hyperextension for 5 weeks. One year later a recurrent deformity of 20 degrees was noted.

CASE 9. A boy (D. L. 1351) of 3 years had very extensive paralysis at age of 6 months. During the subacute stage he was hospitalized for a period of 10 months with protection and muscle training. Considerable improvement was obtained in arms, but very little in trunk and legs. Four months after discharge he was found to have developed a flexion deformity of the hip, and 7 months later he was readmitted and a fasciotomy performed. Correction was maintained for 7 months, but when examined 16 months after operation a recurrence of deformity was noted.

Two other cases, although not representing failures, are of interest.

A 5 year old boy (H. W. 690) had an acute attack when 3 months old. At operation he presented a hip flexion deformity of 45 degrees which was corrected. One year later the deformity showed a slight tendency to recur and home stretching was instituted. No deformity developed and he has maintained full correction for 7 years.

One girl (M. L. 438) of 15 years with extreme paralysis of 8 years' duration showed a bilateral deformity of 90 and 70 degrees. She had been operated on for a similar deformity at the Boston Children's Hospital 8 years previously. She had a combined procedure on the right, and a simple fasciotomy on the left and was stretched for 10 weeks. There is full correction 2 years after operation, but she stands with extreme lumbar lordosis and complains of intermittent low lumbar backache.

DIVISION OF ILIOTIBIAL BAND AND TENOTOMY AT THE HIP

Open division of the iliotibial band as previously described was combined with subcutaneous tenotomy of the structures attached to the anterior superior iliac spine 28 times in 22 children. These were largely cases in which the first procedure failed to give satisfactory immediate correction, but where the remaining deformity was thought to be insufficient to demand the complete division of an open fasciotomy. In these cases, the age varied from 2 to 14 years, with half under 6 years and three-quarters under 9. The duration of paralysis from 1 to 6 years, with half 4 or more; and the amount of deformity in 17 recorded cases varied from 20 to 60 degrees with half 45 degrees or more. Twenty four operations in 19 cases are available for follow up, having been observed for 1 year in 8 cases, 2 years in 10 cases, and 3 years after operation in 6 cases. Nine cases (37.5 per cent) in 7 children showed recurrence of deformity.

CASE 1. D. P. 1056 has been cited under division of the iliotibial band.

CASES 2 and 3. V. B. 1373 see under hip fasciotomy.

CASE 4. A girl of 19 months (H. P. 2237) with paralysis of 16 months, had this procedure followed by 8 weeks of stretching. This, however, was found to be inadequate to secure complete correction and a fasciotomy at the hip was done. Correction has been maintained for 1 year.

CASE 5. A 3 year old boy (C. G. 1267) with no definite history of the acute attack was corrected by this method and maintained correction for 2½ years when slight recurrence was noted. Muscle test showed poor extensors and fair flexors. During the next year the deformity did not increase.

CASES 6 and 7. Another 3 year old boy (A. L. 1346) with paralysis for 2 years, presented 25 degrees deformity in both hips. These were corrected, and correction maintained for 1 year and 10 months when recurrence was noted of 5 to 10 degrees on the right and 20 degrees on the left.

CASE 8. A 9 year old boy (W. H. 1466) with paralysis for 3 years presented a 45 degree deformity. Muscle test showed absent extensors and good flexors. He was stretched for 4 weeks following correction. One year later a deformity of 10 degrees had recurred. Two years after operation a second correction was done by a hip fasciotomy and this has been maintained for 2 years.

CASE 9. A boy (A. S. 1318) aged 12 with paralysis of 4½ years, had been admitted with a flexion deformity of the left hip 1¼ years previously which had been corrected by open division of the iliotibial tract combined with a subcutaneous fasciotomy at the anterior superior spine. He was stretched for 4 weeks after operation. Nine months later a recurrence of abduction deformity was noted, and 15 months after the first operation, a second correction was done by a hip fasciotomy. This correction has been maintained for 2 years. Muscle test before the second operation showed good extensors and trace in flexors, but no adductors.

DIVISION OF ILIOTIBIAL BAND AND HIP FASCIOTOMY

Open division of the iliotibial band and open fasciotomy of the hip were combined 45 times in 37 children. These represent on an average older children, with paralysis of longer duration, and more severe deformity. The age varies from 2 to 15 with three-quarters 8 or over, approximately one-half had paralysis more then 5 years.

The amount of deformity was mild or less than 30 degrees in 6 cases, moderate or 30 to 59 degrees in 21 cases, and severe or 60 to 90 degrees in 13 cases. The period of postoperative stretching in 33 hips varied from 3 to 14 weeks, being usually 4 weeks.

Forty-two operations on 35 patients have been followed for more than 1 year. The period of observation has been 8 years in 2, 7 years in 4, 6 years in 4, 5 in 2, 4 in 6, 3 in 10, 2 in 6, and 1 in 8 cases. There have been 5 recurrences in this group, or an incidence of 12 per cent.

These failures were as follows:

CASE 1. A girl of 3 years (C. S. 1010), with paralysis for 1½ years and 25 degrees deformity. The extensors were poor and the flexors good. She was stretched for 4 weeks after operation. A recurrence of 15 degrees was noted between 2 and 2½ years after operation. This was corrected by intermittent stretching at home and remained corrected until 5 years after her original operation when a 10 degree deformity in full adduction was again noted.

CASE 2. A boy of 8 years (D. I. 1548) who had had a paralysis for 5 years, had a 40 degree deformity which was corrected and stretched for 3 weeks. There was no power in either flexors or extensors. One year after operation a deformity of 10 to 15 degrees had reappeared and this has remained constant for 1 year.

CASES 3 and 4. A boy of 8 years (E. A. 1033) with acute onset of his paralysis at the age of 1 year, presented a deformity of 80 degrees on the right and 90 degrees on the left. The only demonstrable hip musculature was poor flexors on the right. Correction was maintained for 2 years on the right and 4 years on the left, before slight recurrence appeared. He had been followed for 4 years and the deformity in the right has not increased.

CASE 5. The details of this case (D. P. 1056) have been given under open division of the iliotibial band.

Another interesting case in this group is that of a boy of 12 years (J. D. 404) with a paralysis of 10 years' standing and a deformity of 60 to 75 degrees who had a similar deformity corrected at the Boston Children's Hospital 7 years previously. He has maintained his second correction for 6 years.

Of particular interest in this series is a group of eight deformities in boys in whom division of the iliotibial band and stretching for from 3 weeks to 4 months (average 6 weeks) was insufficient to obtain hyperextension. These boys then had the fasciotomy done at the hip and have maintained their corrections 8, 7, 3, 2, 4, 1, and 1 years, respectively. At operation they were 9, 9, 15, 12, 8, and 8 with paralysis of 3, 5, 10, 11, 7, and 5 years' standing. The deformity was 60, 45, unstated, 30, 80–90, and 30–35.

ANALYSIS OF FAILURES

Correction was obtained in 168 deformities. Eighteen of these, all of which still show complete correction, are excluded, because they have been observed less than 1 year since operation. Of the 150 remaining cases, which have been followed from 1 to 8 years, 30 (20 per cent) have shown some recurrence of deformity. This recurrence has appeared during the first year in about one-third of the cases, during the second year in another third, and the remainder have been late, 4 at 4 years, 1 at 5, and 1 at 6½ years after correction. The recurrences have been equally divided between the boys and girls, and as the deformity was found more frequently in boys, the index of recurrences is slightly greater in the girls.

In regard to the type of correction there would seem to be evidence that open operations offer better probability of success than subcutaneous divisions.

It is of particular interest that the recurrence did not seem to be influenced by the severity of the deformity, but that the contrary seems to be true. In 22 extreme deformities (60 to 90 degrees)

there were only 3 failures, or an incidence of 13 per cent. In 69 moderate deformities (30 to 59 degrees), there were 12 failures or 18 per cent; while in 23 mild deformities (less than 30 degrees) there were 7 failures, or 30 per cent.

We had also a preconceived idea that the older patients with longer duration of paralysis would probably show greater recurrence. This, however, was not found to be true. In 20 cases correction was done at ages younger than 4 years, and of these 9 showed recurrences, or 45 per cent. Forty-eight cases aged 10 or over showed 10 poor results, or 20 per cent.

In the whole series, 20 per cent were under 3 years, while of the recurrences 30 per cent were of this age. Thirty per cent of the entire group were above 5 years, while 20 per cent of the recurrences were above this age. There is no significant difference of the age of onset of the paralysis in the entire group and in the recurrences.

SUMMARY

1. Hip flexion deformity, which is actually a combination of flexion and abduction, is a disabling and common complication of infantile paralysis, occurring in 19 per cent of 622 cases seen at this clinic.

2. It may occur alone or in combination with other deformities. Some other deformity corrected at the same time was present in 62 per cent.

3. In this series the ratio of male to female is 60:40.

4. The deformity may occur at any age during childhood, and may appear early in the disease. although most commonly seen 3 to 5 years after onset. The deformity may increase up to 90 degrees of flexion.

5. Five methods of correction have been employed, combined to form eight groups, namely; stretching; subcutaneous tenotomy at the hip; subcutaneous tenotomy of the iliotibial band; this procedure combined with fasciotomy at the hip; open division of the iliotibial band; this combined with subcutaneous tenotomy at the hip; the same combined with fasciotomy at the hip; and fasciotomy at the hip alone. Over 95 per cent of the cases encountered are included in the last four groups.

6. Stretching is considered a factor of great importance in the postoperative care of the patient.

7. The standard accepted for a good result has been complete extension in both adduction and abduction for at least 1 year following operation.

8. The results obtained have been as follows:

Stretching, 2 cases. Available for result study, 2. Good results, 1, 50 per cent. Poor results, 1, 50 per cent.

Tenotomy at hip, 3 cases. Available for result study, 1. Good results, none, 0 per cent. Poor results, 1, 100 per cent.

Tenotomy of iliotibial band, 2 cases. Available for result study, 2. Good results, 2, 100 per cent. Poor results, none, 0 per cent.

Tenotomy of iliotibial band combined with fasciotomy at the hip, 3 cases. Available for result study, 3. Good results, 3, 100 per cent. Poor results, none, 0 per cent.

Open division of iliotibial band, 40 cases. Available for result study, 35. Good results, 30, 86 per cent. Poor results, 5, 14 per cent.

Open division of iliotibial band combined with tenotomy at the hip, 28 cases. Available for result study, 24 cases. Good results, 15 cases, 62.5 per cent. Poor results, 9 cases, 37.5 per cent.

Hip fasciotomy combined with open division of the iliotibial band, 45 cases. Available for result study, 42 cases. Good results, 37 cases, 88 per cent. Poor results, 5 cases, 12 per cent.

Total group, 160 cases. Available for result study, 150 cases. Good results, 120 cases, 80 per cent. Poor results, 30 cases, 20 per cent.

Combined figures for major procedures, 158 cases. Available for result study, 140 cases. Good results, 114 cases, 80 per cent. Poor results, 28 cases, 20 per cent.

9. Each case should be considered individually for the selection of proper procedure.

10. In view of the fact that the original causative muscle imbalance is not altered we feel that this is a high proportion of satisfactory results. Moreover, the degree of muscle loss and muscle imbalance is apparently not the determining factor in recurrence.

11. Milder deformities and young children have shown a higher percentage of recurrence than severe deformities and older children.

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OSTEOMYELITIS IN INFANTS

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EXPERIENCE with more than 300 cases of the subacute and chronic forms of osteomyelitis leads me to the conclusion that this disorder in the acute state is rarely accepted as a clinical entity by the profession; that in practically every instance it remains unrecognized and is therefore neglected in the early stage when treatment would do most to prevent unfortunate sequelæ.

The same was true of appendicitis; before it was recognized as a common clinical entity, a similar period of defection elapsed, but the disease was so prevalent and the leaders in surgery continued to emphasize the characteristic symptoms until finally the syndrome has become so definite that even the average layman has come to know that if a person is seized with pain in the belly with vomiting and localization of the pain in the right lower quadrant, and with elevation of temperature, that person in all probability has an acute appendicitis and the appendix should be removed. At least it may be said that today almost every practitioner of medicine, upon finding localized tenderness in McBurney's point and leucocytosis, properly advises appendectomy. Popular misinformation has even led to the expression that unless the appendix is removed the patient will die—an error, of course, in most instances, for there is reason to believe that in most cases, the condition would resolve.

There is little reason to expect such good fortune in the early recognition of acute osteomyelitis which, though the outcome is seldom fatal, does demand, in nearly every instance, surgical interference or else the victim becomes a subject of prolonged invalidism, the duration of the invalidism being in direct ratio to the delay in the recognition of the condition in the acute stage. I believe that this disease causes as great morbidity and crippling as does tuberculosis of the joints or infantile paralysis. It is needless to point out the reasons, chief among which is error in diagnosis. This may be traceable to the fact that the disease is relatively rare, in so far as a single practice is concerned, to the absence of objective phenomena, and to the negative X-ray findings at the onset.

In the propaganda for reform in the handling of this malady we should enunciate a dictum analogous to that in acute appendicitis, and as teachers of surgery we should reiterate this dictum until it is established upon a traditional basis. This dictum should be stated as follows: If a child under 13 years of age is seized with pain in an extremity, and he shows loss of function, elevation of temperature, and leucocytosis, that child has acute osteomyelitis. Any other entity such as acute arthritis, acute articular rheumatism, neuritis, poliomyelitis, is improbable. In such a picture the obligation of the doctor is to determine the point of localized tenderness over the end of a long bone, and, upon recognition of this point of tenderness, to open the cortex and drain. This seems axiomatic to the orthopedic surgeon of experience who seldom sees these patients until the sequelæ incidental to neglect are in evidence, namely: extensive bone necrosis, multiple metastatic lesions ensuing upon the primary one—in the hip and elbow septic arthritis, fracture, and deformity—parenchymatous and cardiac lesions, secondary anemia, to say nothing of deformities due to disorders of bone growth. The dictum should be disseminated to the general practitioner.

The difficulties met in these cases are several. One is in the contention of the child that the pain is in a joint when it really is not, and here we must utilize art and skill in the segregation of bone from joint. Too little stress has been laid upon the fact that a joint adjacent to a bone which is the seat of acute osteomyelitis becomes distended by effusion of fluid rich in leucocytes that looks like pus but is sterile. This leads to the diagnosis of septic arthritis and drainage, hence infection of the joint; the surgeon is lulled into a feeling of accomplishment, the real focus is neglected and great harm results. It should be remembered that in acute osteomyelitis of a vertebral body, similar effusion occurs into the spinal canal and may be associated with symptoms of meningeal irritation.

Another pitfall is the disparity between the subjective phenomena and the visible or palpable finding: no swelling, no redness, negative roentgenograph; only *localized tenderness* and that difficult to localize. If the child is old enough and the examiner adroit the area of tenderness can be determined.

The degree of pain and the loss of function and elevation of temperature may be confusing, because it varies with the nature of the invading organism, the age of the bone involved, and the resistance of the child.

Great, indeed, are the difficulties when the child is too young to co-operate in localizing the area of tenderness, and the examiner is left to more intuitive resources. Fortunately, however, delay is less injurious in the young child than to the older one. Of the greatest importance, in the child of 15 or over, is the very early drainage because in such patients the traditional reliability of the epiphyseal cartilage to resist invasion to the adjacent joint has become impaired because the cartilage is thinner, at that and greater ages.

Acute osteomyelitis is a disease exclusively of children; i.e., it is a hematogenous infection lodging in the end arteries and stagnant venous sinuses of the growing epiphysis. These latter do not exist in the adult bone and vary at ages in childhood. It would appear that osteomyelitis supervening in an adult is in all probability a lighting up of an ancient quiescent process acquired in childhood. The arteriovenous arrangement seems to be especially adapted to the development of infection between the ages of 5 and 11 years. Fortunately, the epiphyseal cartilage is thick at this time and is nearly always competent to prevent extension of infection to an adjacent joint; neglected disease will rupture through bone periosteum, fascia, and even skin, and leave the joint unimpaired. However, at the upper end of the femur and the lower end of the humerus, the epiphyses and the adjacent diaphyses are inside the joint capsule of hip and elbow, respectively; hence, rupture near the epiphysis is into the joint so that septic arthritis ensues. However, even in these, direct approach to the bone lesion early, even through the joint, will save the joint.

As previously referred to, in the older child, 16 to 18 years, the epiphyseal disc is thin (bone growth having been nearly completed) and may thus enable jointward extension. It may well be stated, therefore, that acute osteomyelitis becomes progressively a more urgent and serious problem with the increased age of the patient.

In a consideration of the subject as a whole, a correlation of the pathogenesis and subsequent changes with the clinical evidences is necessary, and in our series the following facts have been driven home by repetition:

In the prevalent age:

1. Boils on the skin are the most frequent primary focus, otitis media next.

2. The onset is abrupt, with pain usually in an extremity for which no sufficient cause can be assigned (although usually a history of trauma), associated with fever and leucocytosis.

3. Pain is constant and is not relieved by rest to the degree that would obtain in a joint lesion.

4. Loss of function of the extremity occurs to a curious degree; there is no muscle spasm as in a joint lesion. The extremity lies limply and movement passively is resented, although it can be done painlessly. This may readily cause confusion with poliomyelitis.

5. A joint infected cannot be moved a single bit without great pain. A joint seemingly but not really the seat of infection and near a focus of osteomyelitis can be moved passively carefully and painlessly.

6. Localized tenderness in a joint process is definitely around the edge of the articular ends of the bones. In osteomyelitis it is not there, but at the diaphyseal side of the epiphyseal cartilage.

7. Absence of those other phenomena so firmly intrenched in our minds as necessary evidences of inflammation; viz., swelling, heat, and redness, and absence of X-ray evidences. It is too early; these are all present but inside an unyielding tube —hence, not discernible.

8. In long bones of the extremities, the picture is sufficient and calls for removal of a window of bone and drainage. The prognosis is excellent. In 3 weeks general radiographic study of the whole skeleton is justified as well as clinical study for secondary foci which, because of immunization of the subject, are subacute in their evidences and hence easily overlooked.

9. The primary drainage is seldom final as bone necrosis will occur necessitating later ablation in from 8 to 12 weeks.

10. In the definitive treatment, the object to be attained is radical excision and obliteration of the defect surgically, for which no substitute, such as antiseptics, injections, or maggots will ever do.

11. Bones imbedded too deeply for palpation present a more difficult problem and may be incapable of diagnosis until X-ray evidences are available or abscess supervenes. However, in acute febrile and painful disorders of the abdomen in children, one should remember that the lesion may be somatic instead of visceral. The crest of the ileum, anterior superior spine, anterior inferior spine of the ileum, and the tuber ischii are common sites. I have seen several patients with acute osteomyelitis of the pelvic bones upon whom abdominal operations have been performed for acute appendicitis, ileus, and what not; and in the thorax, osteomyelitis of a rib with extraplural abscess thought to be empyema thoracis.

12. In the vertebra, sacrum, and some widely disseminated lesions, one is sometimes stumped by the insolubility of the problem.

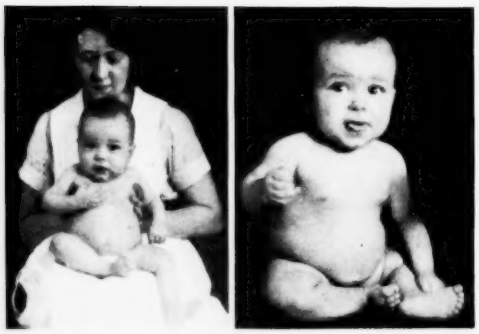


Fig. 1, left. Case 1. On admission. Osteomyelitis left femur. Note evidence of loss of function of left lower extremity.

Fig. 3. Case 1. On discharge.

So much with reference to the general aspects of the disorders at the common age of incidence. These remarks are prefatory to the report of cases in infants, affording opportunity to contrast the manifestations therein to that at the usual ages. Someone has said that infants under 1 year are immune, and judging from the available literature on the subject, osteomyelitis is very rare in infants or else is usually overlooked altogether, and I am inclined to suspect the latter as the reason for the supposed rarity.

Indicative of the paucity of reference in the literature is the fact that a survey thereof for the last 18 years discloses few articles mentioning it, and only 1 case of acute osteomyelitis of a long bone in an infant is definitely reported.

Wade, in an article on osteomyelitis in children states that the incidence is from birth to 3 months then none until 2 years, but presents no specific case in an infant.

E. Marx reports 36 cases in the maxilla seemingly associated with mastitis in the mother, impetigo, and a habit of mothers of putting their fingers in infants' mouths.

Madier reports an acute case involving the vertebræ in an infant of 3 weeks.

Baumgartner reports a case in the skull.

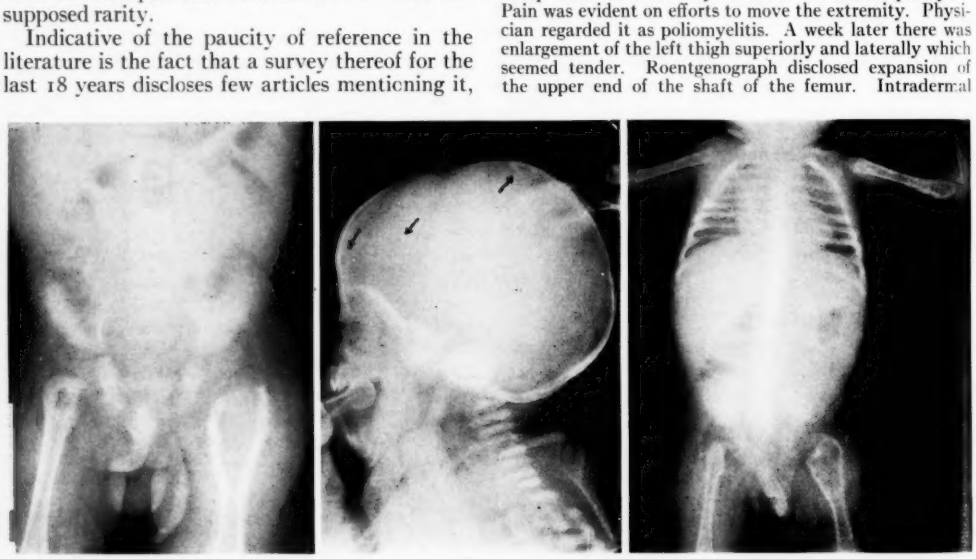
Karplus reports a case affecting mandible and tibia.

Pyrah and Pain, reviewing 262 cases, mention in the age incidence 6 cases under 1 year of age, but no specific reference is made to their course.

It is thought that the disease in early infancy constitutes an entity of such clearness as to set it apart from the ordinary picture at other ages.

The reports of 3 cases in infants under 6 months of age follow:

Case 1. J. R., aged 6 months, was admitted to the hospital April 15, 1930. Child had been perfectly well until the age of 4 months when without apparent cause became fretful and irritable and developed temperature of 100 degrees F. In 3 or 4 days the left lower extremity began to droop and showed every evidence of flaccid paralysis. Pain was evident on efforts to move the extremity. Physician regarded it as poliomyelitis. A week later there was enlargement of the left thigh superiorly and laterally which seemed tender. Roentgenograph disclosed expansion of the upper end of the shaft of the femur. Intradermal



a b c

Fig. 2. Case 1. a, Note periosteal expansion of upper one-half of left femur and loss of normal conformation of the bone and circumscribed area of distinction in upper end of right femur. b, Skull lesions. c, General view of trunk and extremities. Note lesions in both femora, lower end of left humerus, and opacity in mediastinum on right

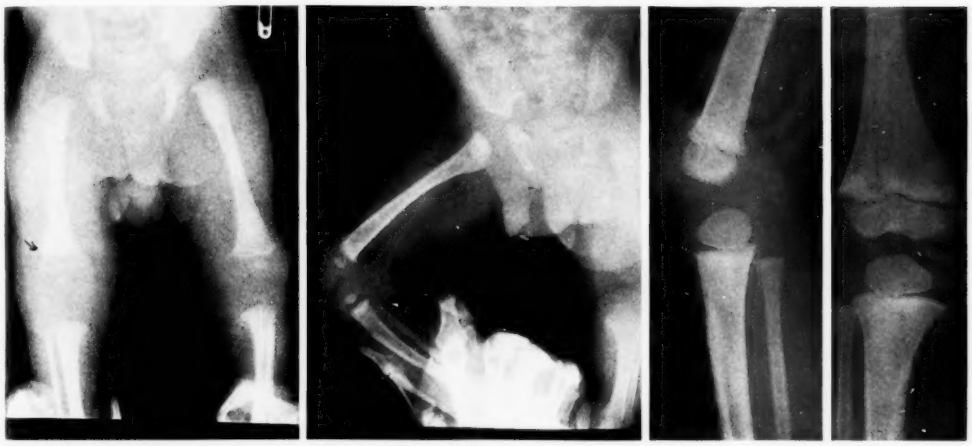


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Fig. 4. Case 2. a, General increased opacity of right thigh soft structures. Area of decreased opacity at metaphysis of femur. b, Six weeks after operation. c, Two years after operation.

tuberculin tests were negative. History of lues in both parents led to suspicion of syphilitic osteitis but appearance was more suggestive of osteogenic sarcoma.

The child came to the hospital 1 month after the onset. General appearance good (Fig. 1) although had lost several pounds, had continuous cough, with temperature 101 degrees. Appetite was good. Physical examination throughout was negative except for (1) left lower extremity which hung loosely without voluntary motion at hip or knee, although the foot was elevated upon plantar stroking. The left thigh was enlarged throughout its length, felt baggy and seemed to be tender but not greatly so. No fluctuation was elicited. Movements at hip and knee could be carried out passively gently, without pain. (2) Over the left parietal aspect of the skull there was an elevation circumscribed as large in diameter as a dollar, seemingly fluctuant.

Roentgenographic findings. Figure 2a, femur, left. The upper one-half was expanded and pear-shaped with thin cortex and cavitation as in bone cyst or giant cell tumor. The upper half of shaft was evidently dissolved away and the periosteum had been elevated. The lower half of shaft appeared normal. No evidence of hip joint destruction was present. Right femur disclosed in the neck a circumscribed area of increased radiability, a cavity without periosteal reaction.

Figure 2b, skull. Three circumscribed areas measuring 1 centimeter in diameter, simulating cystic disease were present in vertex and parietal bone anteriorly.

Figure 2c, general view of trunk. In addition to changes noted above, left humerus disclosed in its lower third periosteal elevation and expansion of the bone and a cavity circumscribed in the distal end of diaphysis. The chest revealed an area of decreased radiability in the mediastinum to the right and above the cardiac shadow, evidently either hilus thickening or inflammatory process in the mediastinum.

Other laboratory findings. Urine, negative. Blood: hemoglobin, 66 per cent; red blood cells, 4,020,000; white blood cells, 23,400; neutrophiles, 46; lymphocytes, 50; eosinophiles or large mononuclears, 2; Kolmer, negative.

In the light of the multiplicity of lesions, the abrupt onset and evidences of febrile nature with abscess, the conclusion was reached that the diagnosis of acute osteomyelitis was justified. Neoplasm was ruled out by the multiplicity of lesions and the fact that the child was not old enough for a neoplasm to have reached the size noted unless beginning before birth. Fibrocystic disease might be suspected from certain X-ray aspects alone; however, nothing other than a hematogenous infective process could fill all requirements in the diagnosis.

Aspiration was done in the parietal bone swelling and no fluid secured; the left femoral mass yielded grayish yellow purulent material which upon smear and culture was negative.

Operation. In the light of continued elevation of temperature and leucocytosis and seeming deep fluctuation and aspirated fluid, exploration of the left femur was done. In the soft parts a small quantity of watery purulent material was evacuated, and the bone was exposed at the site of expansion. The cortex was thin and softer than eggshell. A window was removed and the cavity found hollow and not trabeculated and contained a few cubic centimeters of serosanguineous fluid. No sequestra were found. A small rubber wick was inserted and removed in 3 days, followed by very rapid closure.

Culture and smear of fluid were negative; bone tissue, recent periosteal bone.

The recovery was rapid and uneventful. The general nutrition rapidly improved. Temperature gradually subsided. No clinical evidence of the lesions was noted other than at the left femur which gradually subsided in swelling and resumed movements and normal contour and complete recovery to normal.

The patient had acute hematogenous osteomyelitis, the lesion became sterile, and rapid restitution of damaged bones resulted. Upon discharge from the hospital June 6, 1930, less than 3 months from admission, no clinical evidences remained (Fig. 3).

Roentgentograms taken recently, but not available, disclose no abnormalities in the skeleton.

Case 2. E. W., aged 4 weeks; normal delivery. Circumcision was done at end of 1 week; no infection.

Fig. 5.

Fig. 6a.

Fig. 6b.

Fig. 7.

Fig. 5. Case 3. Appearance of left lower extremity on admission to the hospital. A fluctuating swelling over patella and general swelling of the knee with flexion are exhibited.

Fig. 6. Left knee. a, Generally increased opacity of knee joint sensations. Patella not ossified. b, Five weeks after operation. No evidence of disease.

Fig. 7. Case 3. Four weeks after operation.

Pustule occurred on mesial aspect right thigh at age of 2 weeks. Restlessness and irritability at 2½ weeks, associated with loss of function of left lower extremity.

On admission to the hospital, temperature was 102 degrees. Right lower extremity hung as if paralyzed. The lower end of the femur looked and felt as if there was little general swelling. Pressure over the distal end of shaft on the lateral aspect over the epiphysis seemed to cause pain and was evidently the seat of maximum localized tenderness. Leucocytes numbered 22,000. The evidence was sufficient to enable a diagnosis of acute osteomyelitis of femur. A needle was inserted at this point to the bone and a few drops of thin pus were withdrawn.

X-ray findings. Right thigh: General enlargement of soft parts and increased opacity from hip to knee. Small, irregular area of increased radiability in the lower femoral diaphysis laterally just proximal to epiphyseal disc (Fig. 4a).

Operation. At age of 4 weeks, an incision was made at the lateral aspect of the lower end of the femur, and a small abscess was found deeply superficial to the bone. The periosteum found to be loose and elevated by pus from within. The periosteum was opened freely. The bone was not entered. One small gutta percha drain was inserted and hot wet dressings were applied.

There was immediate and rapid improvement. The drain was removed in 1 week, during which time the discharge from the wound was moderate. The wound closed at the end of 3 weeks and function gradually returned, temperature subsided, and all evidences of disease disappeared within 5 weeks.

Culture of fluid disclosed Staphylococcus aureus.

Radiographic examination 6 weeks after operation (Fig. 4b) revealed little expansion of bone at the epiphyseal border of the diaphysis of the right femur at the lower extremity. No evidence of bone disease within. Two years later the child revealed no evidence of abnormality. Radiograph (Fig. 4c) disclosed normal bone structure with a little projection of bone from the diaphysis just above the epiphysis—the remains of the old elevation of periosteum.

CASE 3. S. M., aged 5 weeks. On admission to the hospital no history was available except that for 10 days baby had been fretful and "feverish." One week before admission, child lost function of the left lower extremity which began to "draw up."

Temperature was 102 degrees. Patient was a markedly malnourished infant, skin dry. Left lower extremity was without voluntary movements. The knee was flexed above 90 degrees, and in the prepatellar area was a circumscribed swelling which was hot and red and fluctuant (Fig. 5). The knee could not be extended passively.

Roentgenogram on admission (Fig. 6a) revealed in addition to marked flexion of the knee, general increased opacity of the soft structures of the joint. No definite bone pathology was evident.

A diagnosis of probable acute osteomyelitis of the patella was made.

At operation a needle was inserted into the fluctuant swelling and yielded 1 cubic centimeter thick yellow pus. An incision was made anterolaterally toward the patella, and 4 cubic centimeters of pus was evacuated. Vertical traction was applied to extend the knee.

On culture the fluid disclosed short chain streptococcus.

Drainage was profuse, the knee gradually extended, and all evidence of inflammatory process subsided within 4 weeks, and complete and evidently painless motion of the knee returned, with rapid healing of the wound and general improvement (Fig. 7).

On discharge 5 weeks after admission, roentgenograph (Fig. 6b) disclosed no disease except some opacity of the soft structures of the joint. The patella was not ossified sufficiently to cast a shadow.

There was no indication of any intra-articular process and upon the basis of the location of the lesion and the seeming source of the pus, it appeared that the focus was in the patella.

One cannot help but be impressed in these cases by the general appearance of well being in Case 1 despite numerous untreated foci of osteomyelitis, the marked degree of loss of function of the entire extremity in all of them, the rapidity of resolution upon simple drainage, and the absence of subsequent bone destruction and sequestration.

SUMMARY AND CONCLUSIONS

1. Attention is called to the fact that acute osteomyelitis is rarely diagnosed sufficiently early to avert extensive destruction and complications.

2. Particular attention is directed to the fact that the disorder in infants is rare; at least, there is a dearth of evidence that it is recognized if the number of cases is more than is supposed.

3. Three cases in infants under 6 months of age are reported, 2 of which are under 6 weeks of age.

4. The clinical picture of the disease in infants is contrasted with that in the usual age of incidence with the conclusions that:

a. The disease is rare in infants.

b. It is relatively benign and neglect to treat it in infants is less harmful than in adults.

c. Loss of function is singularly manifest.

d. Drainage alone appears to be adequate treatment.

e. Foci of infection may become sterile.

f. Spontaneous resolution without treatment may occur.

g. Sequestra do not form.

h. The prognosis is favorable.

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MESENTERIC VENOUS THROMBOSIS

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MESENTERIC vascular occlusion and its sequelæ have occupied man's attention for three quarters of a century, but nearly all published work has emphasized the arterial form of the disease, obscuring the less common venous variety. Everyone is familiar with the dramatic series of events which follows the breaking off of an embolus from the heart or aorta and its lodgment in the mesenteric artery, but not everyone is aware that violent abdominal pain, ileus, and collapse may mean mesenteric vascular occlusion, even though the patient have no signs of cardiovascular disease. For this reason we are presenting 2 new cases of intestinal obstruction following thrombosis of the mesenteric veins, an analysis of 70 cases collected from the literature, and a general review of work on the subject published between 1913 and 1933.

HISTORICAL

Interest in this subject really dates, as it does with so many, from Virchow's presentation of his first case of occlusion of the superior mesenteric artery in 1847. Litten, Karcher, Chiene, Kussmaul, Gerhardt, and many others reported cases, emphasized clinical points, and experimented with this peculiar type of intestinal obstruction, and in 1899 Welch and Mall published a thorough experimental study of the entire subject. Jackson, Porter, and Quinby collected all of the available cases from the literature in 1904, added 26 new cases, and made a critical analysis of all of the theoretical and practical work which had been done up to that time. Welch's section on the diseases of the blood vessels in Allbutt and Rolleston's *Surgery* in 1909 restated his former work with some modifications in the light of further investigations.

In 1913 Trotter published his Cambridge monograph in which he brought together all the work done since 1847, and reported 360 cases from his own series and from the literature. Since then the number of cases and the volume of writing on the subject has increased tremendously, but we felt that the occlusions of the superior and inferior mesenteric veins should be treated separately and a review made of the present status of the disease in spite of, or even because of, its clinical similarity to embolism of the mesenteric arteries.

PATHOLOGY

The mechanism of intestinal infarction has been the subject of great controversy since the first case was reported, and even yet is not entirely solved. Exact experimental reproduction of the *in vivo* processes is almost impossible, and the results have not been too gratifying; however, a fairly logical explanation is possible and the following presents a brief résumé of current opinions.[1] That it is conducted from the standpoint of arterial occlusion does not invalidate our avowed purpose of considering only venous occlusion, for the two processes are similar in their end-results and the same conditions affect them both; besides, only in this way can we keep any parallel to other papers written on the subject.

At first thought it would seem that infarction of the intestine should be an extremely rare occurrence because of the extensive anastomoses present in the mesentery, and that when it did occur it should follow the rules laid down by Sprengel that occlusion of an artery gives an ischemic infarct and occlusion of a vein a hemorrhagic one. Neither of these things is true; the disease is relatively not rare and both forms of occlusion cause the hemorrhagic infarct, with very rare exceptions; it is the explaining of these paradoxes which has proved so difficult.

The superior mesenteric artery springs from the front of the aorta beneath the pancreas and rapidly divides into many branches which supply all of the small intestine and about one half of the large. Between these branches run connecting channels parallel to the bowel forming a series of from one to five arcades, depending on how far down the small intestine one goes. From the last arcade run straight vessels, the vasa recta, which arboresce in the bowel wall. Older writers state that the vasa split to encircle the gut and that they anastomose with their neighbors there. Cokkinis' injection experiments[2] showed that this is not true; each vessel supplies but one side of the bowel and does not connect with its companions on either side, although there is considerable overlapping of their branches. He also confirmed previous findings that the superior mesenteric artery has practically no anastomoses with other vessels, and that the veins of the mesentery

[1] Unfortunately in such a composite as this, credit cannot be given for any specific item save in rare instances.
[2] The diagram of Cokkinis illustrates this point with great clarity.

follow the arterial distribution closely throughout except for the region supplied by the ileocolic artery where the veins do not form an ileocolic vein but are direct primary origins of the superior mesenteric vein. These observations give anatomical confirmation to Litten's statement that the superior mesenteric artery, although not strictly an end artery, still behaves like one. With sudden occlusion of either the main stem of the vessel or of two or more vasa recta, blood should be cut off completely from all or a part of the bowel wall, but it is not apparent why infarction should occur with occlusion of one of the intermediate branches. To explain this, two other peculiarities of the bowel circulation must be taken into consideration. The pressure in the mesenteric circulation falls quite rapidly and adequate circulation through the last arcades and terminal branches is largely dependent upon impetus derived from peristaltic movements. Now one of the first responses of the intestine to interference with its oxygen supply is tonic contraction, a response which not only completes the ischemia of the part by sheer muscular pressure on the small intramural vessels but by interfering with peristalsis causes stagnation of the blood stream and induces extension of thrombosis, edema, and extravasation of blood.

Thus we see that the location of an occlusion is of the greatest importance, followed closely by the time factor. If a sudden closure of the main stem of the superior mesenteric artery occurs above the point where any of its branches come off, there will in all probability result an anemic infarct of the entire small bowel and part of the large bowel; if the vein should be closed at this same point, an hemorrhagic infarct of the same territory will follow. These lesions have been observed a few times both clinically and experimentally. A slow closure at the same point may result in infarction, in temporary symptoms of pain and intestinal hemorrhage, or even in no symptoms at all if the occlusion progresses slowly enough for the collateral channels to open out and carry the load. This is evidently what had happened in the oft quoted cases of Virchow and Karcher, who found at autopsy the superior mesenteric artery represented by a solid fibrous cord although the patient apparently gave no history of intestinal disease.

If, now, the occlusion takes place anywhere below the splitting of the artery and above the last arcade, there are several possibilities to be considered. Ligations in this region have generally produced no symptoms at all or at most transitory ones, and in Cokkinis' injections such ligations did not prevent the injection fluid from reaching any part of the gut. If the disturbance produced in the bowel by the initial trauma is of sufficient severity, it may during prolonged tonic spasm cause either marked changes in the bowel wall or by stagnation induce secondary thrombosis in the mesenteric vessels distal to the point of initial occlusion, with permanent vascular isolation of that segment. It is this latter process which Cokkinis feels is responsible for many of the infarctions following localized embolic occlusions in the middle of the mesentery. But here again, if the occlusion is slow enough the spasm will never occur, secondary thrombosis will not develop, a rearrangement of circulation will take place, and the patient will ultimately recover (in fact, may never have symptoms). Of course, with the elaborate by-pass system of the mesentery, back flow must occur into any such territory, or in the case of the venous occlusions inflow from the arterial side; and so in both cases the final lesion will be a thoroughly blood soaked, hemorrhagic infarct.

Finally, occlusions in the vasa recta must cause cutting off of the blood supply to the part, for there are no anastomoses beyond the terminal arcade. However, there is sufficient overlap of the terminal arborizations that occlusion of one vessel will seldom if ever cause trouble; experimentally the vessels supplying about 3 centimeters of bowel must be affected before infarction occurs, and clinically the smallest lesions are of about that size.

As we stated before, much the same laws, conditions, and processes apply to the channels carrying blood away from the part as to the supplying arteries, the only differences being the time factor and the possible occurrence of back pressure on the venous side from an obstructed portal circulation. Arterial occlusion is almost always a sudden embolic affair; venous occlusion a slower thrombotic process. In this connection there is one point of great importance which we feel has not been stressed sufficiently by former writers: that is, that this difference in speed of events may not be obvious clinically. The compensatory powers of the body are extraordinarily great; they may be able to care for a relatively slowly failing circulation without symptoms up to a certain point, but find themselves with dramatic suddenness unable to carry on further, whereupon the typical acute symptoms will appear without warning, although the process has been going on for some time. It is of the greatest importance that the clinician realize this when he is faced with an obscure case of abdominal pain in a young, apparently healthy

person who has no right to an embolus from any cardiac or arterial source.

The pathological changes in the bowel, reported as resulting from one or another stage of this complex mechanism, vary from none to complete gangrene. Edema and congestion of the small submucosal vessels appear to be the earliest noticeable change, followed by increasing degrees of this same process up to marked edema, congestion, petechial hemorrhages, and focal sloughing of the mucosa. The bowel is moderately dilated, dark red in color, heavy, soggy, and filled with thin, bloody, fecal material. Necrosis and gangrene begin at the mucosal surface and extend outward as is shown by cases reported with shining serosa over necrotic muscle and mucosa. However, such a stage is short lived, invasion of the gut wall by intestinal bacteria beginning early and rapidly causing peritonitis. Bloody ascites, probably a tranudate from the congested intestine, is an almost constant finding.

PATHOLOGY OF REPORTED CASES[1]

CASE 1. A male, 67 years of age. The significant findings at autopsy were as follows. The peritoneal cavity contained nearly a liter of foul, yellowish, turbid fluid, in which were suspended large flecks of fibrin. The peritoneal surfaces were injected throughout. The entire small intestine was dilated, with dull, injected serosa and boggy wall. In the midportion of the jejunum were two firm, dark red bands, heavily coated with fibrin, approximately 8 centimeters in length and adjacent to one another. The arterioles of the mesenteric artery of the third order leading to these two points were occluded by small emboli. The midportion of the transverse colon showed a similar dark red, fibrin coated swelling, again about 8 centimeters in length, and the supplying twig of the inferior mesenteric artery was occluded by an embolus. The smaller branches of the superior mesenteric vein were markedly dilated. The proximal 10 centimeters of the superior mesenteric vein itself and the immediately adjacent portion of the portal contained a firm, dark red, friable, adherent thrombus. The liver weighed 940 grams and was markedly irregular in contour, showing an extreme degree of lobulation, with numerous deep, furrowed scars. The color of the lobules ranged from purple to yellow. The aorta was notably calcified and distorted by atheromatous plaques, many of which were ulcerated and overlain by adherent, reddish mural thrombi. In addition, the thoracic aorta was the site of two saccular aneurisms.

Microscopically the small intestine showed congestion and edema of the mucosa with polymorphonuclear infiltration and some desquamation of the lining cells and marked edema and leucocytic infiltration of the submucosa, muscularis and serosa. In addition, the dilated serosal vessels and lymphatics contained numerous polymorphonuclear leucocytes. In the reddened, more indurated portions of the intestine the same changes were noted, together with foci of hemorrhage and more intense polymorphonuclear infiltration of the tissues. The mesenteric arterioles supplying these more intensely involved foci contained occluding emboli made up of agglutinated masses of platelets with a slight amount of fibrin and a few red blood cells. Sections of the mesenteric vein showed an occluding thrombus composed of fibrin, agglutinated platelets, red blood cells, and numerous polymorphonuclear leucocytes, which was adherent to a considerable portion of the circumference of the vessel and displayed a moderate amount of organization by ingrowth of fibroblasts from the vessel walls. In one or two sections, portions of the media of the veins were seen to be necrotic and infiltrated by polymorphonuclear leucocytes. The liver showed the characteristic changes of syphilitic cirrhosis.

Anatomical diagnoses: Gangrene of small intestine with associated acute generalized peritonitis, secondary to thrombosis of portal and superior mesenteric veins; syphilitic cirrhosis of liver; embolic infarction of portions of small intestine and colon, secondary to mural thrombi of aorta. Coexistent but not immediately associated lesions include: syphilitic aortitis, aneurisms of thoracic aorta, acute purulent pericarditis, acute fibrinous pleuritis, old right nephrectomy, fibrosis of islands of Langerhans.

CASE 2. A white male, 51 years of age. The significant findings at autopsy were as follows. Approximately 1 liter of thin, bloody fluid lay in the abdominal cavity. There were several patches of purplish discoloration of the parietal peritoneum. The entire gastro-intestinal tract was ballooned with foul smelling gas and thin fluid, and the small intestine showed marked distention, edema of the wall, and dark purplish discoloration. About 1 meter below the pylorus the jejunum was marked by a pale band approximately 1 centimeter wide. Two and one-half meters further down, the intestine was again marked by a similar band. Between these two points, the intestinal wall was dark purple, edematous, extremely friable, and coated with a thin layer of fibrin. No definite points of adhesion or obstruction could be found, though there were a few old adhesions between the omentum and the visceral peritoneum. In the lower portion of the ileum there was a Meckel's diverticulum 2 centimeters in diameter and 3 centimeters in length. The larger mesenteric veins contained thrombi and there was slight necrosis of some portions of the mesenteric fat.

Microscopic examination showed extreme congestion of the jejunum, with marked edema, hemorrhage, and necrosis. Moderate amounts of fibrin were present as well as some polymorphonuclear infiltration. In some sections the submucosa and portions of the muscularis showed a good deal of increased connective tissue.

Throughout the sections of the intestine there was intense capillary and venous congestion. The superior mesenteric vein contained a pedunculated, fibrin and platelet thrombus adherent to the wall, almost completely organized by ingrowing fibroblasts. Other vessels showed thrombi made up of platelets, fibrin, and red cells, adherent to the wall, with very slight fibroblastic ingrowth. Still others were completely occluded, without organization, by masses of fibrin, platelets, and red blood cells.

Anatomical diagnoses: Thromboses of superior mesenteric vein and its tributaries, with gangrene of jejunum and portion of ileum. Coexistent but not associated lesions include: atheromatous arteriosclerosis of aorta, arteriosclerotic nephrosclerosis, hyalinization of islands of Langerhans.

These 2 cases serve to emphasize the diverse nature of the processes involved in venous mesenteric occlusion, in spite of the similarity in the ultimate results. In the first case we have a probably sudden, massive thrombosis of the portal and superior mesenteric vein, precipitated by stasis in the portal circulation secondary to a

[1] Clinical histories presented later.

badly damaged liver; in the second, we have numerous thrombi of varying ages occurring without any discernible cause, yet in both almost exactly similar changes in the intestinal tract. What part the arterial embolism may have played in the first case is not entirely clear, but was apparently limited to local intensification of the general infarction, and was only a chance occurrence rather than related to the venous thrombosis. The age of the venous process was such as to preclude the possibility of its being secondary to infarction resulting from the arterial embolism, as we have clear cut evidence of some days' duration of the venous thrombosis afforded by partial organization of the thrombus. In our second case we have no known cause for the initial venous thrombosis, but the nearly completely organized thrombus in the superior mesenteric vein, once formed, would have produced marked stasis in the portal circulation and given a basis for the formation of subsequent thromboses. Variation in the time of occurrence of these is easily understood when the diverse factors of venous obstruction and of distention and necrosis of the intestine resulting from impaired circulation are considered. Once the venous return is completely occluded, the changes in the intestine can progress only to hemorrhagic infarction. Since this type of infarction usually also occurs, as we have already pointed out, in arterial occlusion, careful dissection of the mesenteric vessels is essential to establish the nature of the circulatory disturbance.

ETIOLOGY

The etiology of venous thrombosis in the mesentery offers the same problems as thrombosis elsewhere in the body, and probably includes an even greater number of causative factors than in most other locations. As Eliot says, "In a very considerable proportion of cases, no adequate cause can be discovered. That cases of mesenteric thrombosis not infrequently occur without discoverable cause and in patients with no history of previous illness cannot be too strongly emphasized. While the etiological importance—(of certain diseases)—must always be recognized, the fact that, occasionally, not one can be identified must not be overlooked and must not lead to the positive exclusion of mesenteric thrombosis in the diagnosis of acute and subacute obscure abdominal conditions." However, Larson, Reich, Eliot himself, and many others have shown in recent articles that there are several predisposing conditions the existence of which, along with symptoms of "acute or subacute obscure abdominal" distress, should always make one consider the possibility of serious circulatory damage to the bowel. These may be grouped roughly into four major groups: infectious, hematogenous, traumatic, and mechanical.

We do not agree with the customary division into two classes of primary and secondary thrombosis, for the so called primary cases are generally those for which no cause can be found; this does not justify their being classed as primary thromboses to the exclusion of those with definite, traceable etiology. It seems more logical to us to take those cases with known causes, classify those causes, and then admit that there are other cases of unknown etiology, the origin of which may or may not lie within the mesentery itself, and lump them together in a limbo of obscure cases.

Specifically, our first group includes all those cases in which there is a known infection in the region drained by the mesenteric, venous, or lymphatic system, in neighboring loci from which direct mechanical extension of the infection to the mesenteric vascular tree would be possible, or in which general circulatory sepsis exists. We do not agree with Bucura's attempt to include as infectious various hypothetical "toxic" substances present in eclampsia, leiomyoma uteri, normal puerperium, etc. Until definite evidence can be produced, as it has not been so far, that there are such substances which change the nature of the vessel wall in such a way as to induce thrombosis, we see no reason for assuming their existence while there are other factors which can equally well explain the process. We do include in the first group thrombophlebitis, appendicitis, pelvic abscesses, peritonitis, and general sepsis. The second group, that of hematogenous causation, includes blood diseases or changes known to predispose to thrombosis, such as the splenic anemias, and polycythemia vera. The third group, the traumatic, includes thrombosis from any sort of trauma to the mesenteric vessels, tearing of the mesentery, and trauma from abdominal operations. The fourth group, that of the mechanical causes, is rather large, comprising portal stasis, pressure from tumors, and pressure from adhesions or congenital bands across the mesenteric vessels. Relying principally on Moloschin's report of a case in which the occlusion was caused by tumor cells from a liver carcinoma, Reich includes retrograde embolus as a mechanical cause, but his evidence for the occurrence of such a phenomenon we feel to be weak. The cases which he supposes to have such a cause could equally well represent multiple thromboses based on sepsis or mechanical stasis. Because of obvious factors, cases of volvulus and strangulated hernias

TABLE I.—CAUSES OF VENOUS MESENTERIC THROMBOSIS

	Warren and Eberhard	Larson	Cokkinis	Blackburn	Total
Appendicitis	1	5	11	1	18
Enteritis	2	1		1	4
Thrombophlebitis, iliac and femoral	3			1	4
Endophlebitis obliterans			1		1
Ulcerative colitis			1		1
Diverticulitis			1		1
Abscess	1		1		2
Polycythemia	7				7
Splenic anemia and splenectomy	3				3
Hemophilia				1	1
Previous pelvic operations	6		1		7
Pregnancy Abortion Delivery	 2 1			 1	 3 1
Pressure Tuberculous nodes Adhesions	 1 1		 3	 3	 1 7
Ascaris lumbricoides	1				1
Trauma	3		4	1	8
Phlebosclerosis	1				1
Constipation	1				1
Cirrhosis of liver	5				5
Portal thrombosis		4	22		26
Carcinoma of stomach	1				1
Luetic scar of liver	1				1
Unknown	35	6	13		54

have not been included in the category of essential mesenteric thromboses.

In Table I will be found a tabulation of the causes and number of cases attributed to each cause in several series collected since 1913. The table shows considerable differences in the relative frequency of various causes as compiled by different authors, but this is to be expected in such limited lists of cases of a disease with so many possible etiological agents. Perhaps the fairest idea is conveyed by the last column, in which the results of four investigators are combined. The largest group by far is the unknown and perhaps it should be even bigger, for the etiological relationship of many of these conditions is open to legitimate question. For example, how long may a femoral phlebitis be dormant and still hold its place as the source of the later mesenteric thrombosis? After all, there may well be a common unknown cause for both. "Previous pelvic operations" was included because of its occurrence in 17 per cent of our female cases, although in only 2 of these was the thrombosis an immediate postoperative complication; but, in the absence of any other exciting cause, it was felt worth while to mention the possibility of its etiological relationship. In the 3 splenectomy cases, the extension of the thrombosis in the ligated splenic artery was probably the real cause rather than an underlying blood condition. Cokkinis and Larson consider appendicitis of first importance, while Eisenberg and Schlink, and Eliot and Jameson believe that portal thrombosis or cirrhosis of the liver should occupy the honor position. From our investigations we believe that septic abdominal conditions such as appendicitis and pelvic inflammatory disease probably actually account for the greatest number of cases, for many of these probably pass as postoperative ileus or peritonitis and do not find their way into the literature. Next in importance come the cases with hepatic cirrhosis, most of them fatal, nearly all of them discovered at autopsy, and hence, by their very character, forcing themselves on one's attention and so coming to occupy a disproportionately large place among the case reports. One of the most important correlations in the list is that between polycythemia and mesenteric thromboses, Kratzeisen and Jacobi both believing that nearly all cases of the former ultimately die of the latter. Gore suggests that many postoperative patients who exhibit "pseudo-obstruction—a spasm lasting for a few hours or longer" and then go on to recovery are really victims of minor mesenteric thromboses.

At the end of the table is one case which unfortunately had no clinical data to earn it a place in our general series, but as a pathological curiosity deserves mention. This, reported by Weidman, is that of a mesenteric thrombosis following breaking down of a gumma in the right lobe of the liver and abscess formation with thrombosis of the portal and mesenteric veins.

These, of course, still do not represent all of the possible causes of thrombosis of the mesenteric veins, but only give some of the more common predisposing conditions for which the alert clinician will search when confronted with a patient with acute abdominal pain or symptoms of acute intestinal obstruction without obvious mechanical cause.

STATISTICAL ANALYSIS

Any statistical study of this subject must of necessity be open to almost every conceivable error that can beset a numerical analysis of a clinical subject. To gather a group of cases large enough to justify any analysis one must resort, in

TABLE II.—VASCULAR LESIONS OF INTESTINAL VESSELS

No.	Age	Sex	Location of infarction	Artery	Vein	Embolism	Thrombosis	Cause
156	73	F	Jejunum and ileum	+			+	Mechanical (carcinoma)
2760	67	M	Two portions: 8 cm. jejunum, 1 portion colon	(+)	Portal, mesenteric	(+)	+	Cirrhosis of liver
5735	77	M	180 cm. ileum	+		+		Aortic mural thrombi
5917	52	F	125 cm. jejunum	+			+	Mechanical (carcinoma)
6327	60	M	25 cm. ileum	+			+	
15079	73	F	Jejunum and ileum	+		+		
16537	51	M	250 cm. ileum		+		+	
17697	71	F	Jejunum and ileum	+		+		Heart
18168	64	F	Jejunum, mesentery, and ileum	+		+		Heart
18359	72	F	Ascending colon	+		+		Heart
18557	69	M	Jejunum and ileum	+		+		Aorta

this country at least, to the collecting of cases from the literature, and immediately he is faced by the facts that nearly all of the histories are incomplete; there is no standard of observation, interpretation, or treatment; inaccuracies and omissions may exist in the reports, and there are not even definite criteria of what constitutes the clinical entity of essential mesenteric venous occlusion.

Cokkinis obviated some of these failings by taking his material from the records of two very large, old, reputable institutions, and from the private records of men whose ability he knew personally. He was fortunate in being able to unearth as many cases as he did; we miss statistical correlation. Larson's, Ophuels', and Ceelen's reports are excellent but comprise only autopsy material, thus giving no idea of incidence in a general population, mortality rates, or the relative value of different methods of treatment. Robey could not supply the omissions in the records of the Boston City Hospital and thus lost much data which would have been of value. In general, among the individual case reports, Cokkinis is probably right in feeling that the dramatic, successful cases stand a far greater chance of being reported than the obscure, prosaic cases which die without benefit of autopsy or operation, although the latter group undoubtedly forms a large proportion of the instances of this disease.

In Table II we summarize the mesenteric occlusions, both arterial and venous, included in the admissions to the New England Baptist and New England Deaconess Hospitals from 1928 to 1933 inclusive and to the Palmer Memorial Hospital from July, 1927, to January, 1934. The number of cases of vascular occlusion, surgical specimens, and autopsies are taken from the records of the William L. Shearer Pathological Laboratory, through which passes all of the pathological material from the hospitals mentioned, along with a very small percentage of work from other sources.

We have listed in the parallel columns of Table III the general statistical findings of 12 series reported since 1913. The first column is based on Table II. The second column presents the figures gathered by Robey covering a 33 year period. In column 3 are Flynn's results of a 5 year period at the Baylor Hospital. Ophuels', Larson's, and Ceelen's statistics in columns 4, 5 and 6 represent studies on consecutive autopsy series. Cokkinis' figures in column 7 cover a period of 25 years at the London and Guy's Hospitals. Brady's 12 cases shown in column 9 were found at the Johns Hopkins Hospital, while Reich's, L. Miller's, and W. Smith's series consists of cases gathered from the literature with the addition of a few new cases.

The general incidence of venous mesenteric thrombosis is extremely hard to calculate because of the rarity of the disease and the paucity of figures. According to what data we could gather, it is in the neighborhood of 0.003 per cent of the general hospital population and 0.05 per cent of the autopsy populations. Table IV shows the exact figures in the seven available series. Robey, unfortunately, does not give in his paper accurate figures on the occurrence of venous and arterial occlusions, saying, "In our autopsy records there is some differentiation between occlusion of a mesenteric artery and vein, but the former far outnumber the latter." However, although only 5 of his cases are definitely diag-

TABLE III.—INCIDENCE OF MESENTERIC OCCLUSION

	Warren and Eberhard*	Boston City Hospital (by Robey)**	Baylor Hospital (by Flynn)†	Ophuels	Larson	Ceelen	Cokkinis§	Reich	Brady	L. I. Miller	W. Smith	Lankenau Hospital (by Ross)
Admissions	57380		39668									30000
Surgical admissions	26793	206571	27712									
Medical admissions	30587	162574	11956									
Mesenteric occlusion	11	51	2	10	36	5	77	251	12	120	425	
Mesenteric artery	82%	21	50%	90%	55.5%	60%	25%	47%	50%	60.9%	85%	
Mesenteric vein	18%	5	50%	10%	44.5%	40%	75%	53%	50%	39.1%	15%	2
Surgical specimens	19836											
Autopsies	1019			3000	36000	8521						
Mortality (total)		94%		100%	100%	100%			72.5%			
Mortality (operative)		72.7%					83%	80.2%	62.5%			
Mortality (with resection)							58%					

*Palmer Memorial Hospital—1927–1933 inclusive.
New England Baptist and New England Deaconess Hospitals 1928–1933.
**1900–1932 inclusive—25 cases not classified.
†Five year period.
§1900–1935 inclusive.

TABLE IV.—INCIDENCE OF MESENTERIC THROMBOSIS

		W&E	Flynn	Ophuels	Larson	Ceelen	Robey	Ross
Venous:	Hospital population	0.0035	0.0025					0.0066
	Autopsy population	0.196		0.033	0.044	0.023		
Arterial:	Hospital population	0.0157	0.0025					
	Autopsy population	0.88		0.066	0.055	0.035		
Both	Hospital population	0.019					0.014	

nosed as venous occlusion, there are 25 unclassified cases, 18 of which we feel may very well have been venous in character. When the general knowledge of a disease is so poor that a man of as wide experience as Deaver could make this statement in 1929, "Thrombosis of mesenteric arteries may lead to acute symptoms resembling those of acute obstruction, while a venous thrombosis will mimic the more chronic type of obstruction. Very few cases are reported in the literature; those that are described were diagnosed at laparotomy and all of them were fatal"—when such a man could speak thus to a state medical convention without contradiction or comment, then most men are not looking for the disease and many cases must pass unrecognized, so probably the actual incidence is far higher than these figures indicate.

As to the relative incidence of the arterial and venous forms of the disease, Tables III and IV show what wide disagreement exists. Our own figures are undoubtedly misleading because of the very heavy weighting of our material with the diabetic and cardiac patients who form a large percentage of the patients at the Deaconess Hospital. Cokkinis' figures are startling but considerable importance must be attached to them because of the way the cases were collected from which these results were calculated. If our supposition about Robey's figures is true, his venous occlusions would nearly equal his arterials. We may safely say that the relative incidence of venous thrombosis is far higher than we supposed it to be when we embarked on this investigation.

In Table V, the age incidence of venous occlusion is presented. No exactly comparable table could be presented because all other authors have computed their results with all types of mesenteric occlusion lumped together, but the results agree quite well in placing the disease among those of early and middle life, atherosclerosis and cardiac failure forcing the combined tables slightly higher than our series from the literature. The youngest patient we found on record was reported in the monograph of Jackson, Porter, and Quinby, an infant 4 weeks old. Of our cases of known age 44 per cent were under 40.

TABLE V.—AGE INCIDENCE OF VENOUS MESENTERIC OCCLUSION

Years	Cases
0 to 9	2
10 to 19	4
20 to 29	13
30 to 39	12
40 to 49	14
50 to 59	15
60 to 69	10
Unknown	5

TABLE VI.—MORTALITY

	Cases	Alive	Dead	Per cent Mortality
Total number of cases	75	31	44	58.8
Operative cases	55	30	25	45.4
Resection cases	38	25	13	34.2
Cases not operated on	20	1	19	95.0

TABLE VII.—COMPARATIVE MORTALITY

Author	Period covered	Per cent Mortality
Jackson, Porter, and Quinby	1874–1904	92
Trotter	?1874–1913	78
Cokkinis	1900–1926	83
Warren and Eberhard	1913–1933	58.8

TABLE VIII.—DURATION OF SYMPTOMS AND MORTALITY

Duration	Cases	Mortality Per cent
0–12 hours	4	25.0
13–24 hours	12	41.6
25–48 hours	9	71.4
3 days	6	33.3
4 days	6	83.3
Above 4 days	16	78.6

The disease seems to occur with about equal frequency in both sexes, 52.7 per cent of our cases being male, 45.9 per cent female, and 1 case unspecified, but it appears to favor the white race overwhelmingly, all but 2 of our cases being definitely white, 1 negro, and 1 may have been Chinese. This probably merely reflects the hospital populations.

Table VI presents the mortality statistics with some results of treatment. Of the 75 cases reported, 44, or 58.8 per cent, died. Fifty-five were operated on for the lesion and of these only 45.4 per cent succumbed. Thirty-eight were subjected to resection with a mortality of 34.2 per cent. Phrased differently, 31 of the original 75 survived, and of these 30 were operated upon and 25, or 80.6 per cent, had resection. Of the 20 not operated upon, only 1 left the hospital alive.

The effect of more general recognition of the disease, of improved technique in abdominal surgery, and of better recognition of the fact that surgery offers almost the only hope of life that these patients have is well illustrated by a comparison of the general mortality compiled at approximately 10 year intervals. Cokkinis' total figure given here does not give a true representation of the facts because it includes cases back as far as 1900, whereas it is generally recognized that the major improvements have come in the last 15 years.

The tabulation of mortality in relation to the duration of symptoms is extremely misleading because of several factors. The most important one is the characteristic of the disease to proceed with moderate or no symptoms before appearing in full blown form, thus making it often impossible to state the true duration of the disease. We tried to figure in each case the time between the first appearance of really acute symptoms and operation or death, but in many could come to no conclusion at all. Also, the extent of the pathology found may bear no relation to the apparent duration for symptoms; that is, in 1 case patient may have had symptoms for weeks and show relatively little pathological change while another patient who has had symptoms for only a day may show necrosis of the entire bowel. However, from Table VIII and the findings of Cokkinis, Reich, Eliot and Jameson, Larson, Klein, and others, we may say that after the onset of symptoms of intestinal obstruction every hour of delay lowers the patient's chances of recovery. The low figure for 3 days is probably a chance finding dependent upon the chances of such small series, though it may indicate a very slight difference between the fulminating and more chronic types of cases; but this is unlikely.

McIver's monograph on intestinal obstruction brings out several interesting points in this connection. He collected 10 cases of mesenteric obstruction in 335 cases of intestinal obstruction at the Massachusetts General Hospital, studied the relation of interference with circulation to the seriousness of all types of obstructions, and found that such interference raised the mortality from 37 per cent to 53 per cent. He states "—the most important factor governing the pathology and symptomatology, and largely determining the severity of the illness is, paradoxically enough, not the blockage of the intestinal stream but the condition of the circulation to the involved segment of bowel." A case in point is that of Guibal, a strangulation of a scrotal hernia involving several loops of bowel but exhibiting its serious pathology in a thrombosis of several mesenteric veins and infarction of a portion of bowel which apparently was not included in the sac and failing to show any mechanical obstruction of the lumen of the bowel.

SYMPTOMS AND DIAGNOSIS

In 1913, Reich made an exhaustive analysis of the symptoms of occlusion of the mesenteric vessels and worked out an elaborate classification of types of the disease. This has been repeated and modified by numerous writers, notably Eliot and Jameson, Klein, and Wulsten, but while interesting from a statistical and theoretical point of view does not seem to us to accomplish the primary purpose of such work—that is, the clarification of a symptom complex for the benefit of the clinician. Reich believes, as do Loop and others, that there is a definite syndrome aside from the obstructive and peritonitic picture but becomes involved in technical niceties which confuse the picture from a practical standpoint. Ross goes farthest the other way, and says, "The symptoms of mesenteric thrombosis, in so far as they may be grasped, are those of acute intestinal obstruction." Essentially, we are inclined to agree with him, although there are several special features which, if properly evaluated, should help to eliminate the ordinary mechanical obstructions and to point the way to a correct diagnosis and a more accurate prognosis. Cokkinis believes the disease to be diagnosable in about 60 per cent of the cases and states rather forcibly, "—the prognosis and results of treatment will only improve when mesenteric occlusion comes to occupy the important position it deserves in surgery, and its clinical manifestations become sufficiently well known to make early diagnosis possible."

Pain is the presenting symptom in nearly all cases, and previous attacks of abdominal pain, with or without vomiting, may be of great significance. It may be localized or general, and if localized may be in any portion of the abdomen. Early in the disease it is apt to be intermittent or colic-like in character, later becoming rhythmic, and finally merging into the steady, constant pain of peritonitis. It may also migrate, confusion with appendicitis having often occurred because of the appearance of pain in the epigastrium or around the umbilicus with a later movement to the right lower quadrant. The onset is usually sudden and very severe, though there may be premonitory, mild, transient pain before the acute crisis. In a certain number of cases, as in our first case seen in retrospect, these earlier pains may be recognized as representing mild attacks which did not result in sufficient disturbance of circulation to cause obstruction.

Preceding, accompanying, or following the onset of pain there may be vomiting, at first reflex, later obstructive, and finally fecal or bloody. Fecal vomiting is regarded as rare by most writers, though it was stated as being present in five of our cases, but it is always a serious and late sign and one of very bad prognostic import. Hematemesis is somewhat more common, occurring in about 16 per cent of the cases reported. It is considered a highly valuable diagnostic point and of some value prognostically, for it generally occurs rather late and is apt to indicate a lesion high in the jejunum, large in extent, and not amenable to treatment. It may consist of bright red blood, "coffee grounds vomitus," or may be determined only by the chemical tests.

Neither constipation nor diarrhea can be said to be characteristic of the disease, sometimes one, sometimes another, occasionally neither appearing, and often both occurring at different stages of the attack. Cokkinis goes so far as to say that, as in carcinoma of the bowel, "any alteration in the normal action of the bowels" is important. He also believes the enema to be of great diagnostic value, particularly in the cases with constipation where a high enema can wash down what a paralyzed bowel cannot move, and thus will show blood which otherwise would not have been discovered. All writers consider melena a diagnostic point in differentiating between those obstructions with interference to the circulation and those without, again a valuable prognostic help. Strikingly little mention is made of the character of the stool in the case reports which we collected, so that we are unable to draw any conclusions as to its frequency from our own series; but it is generally stated to occur in about 30 per cent of the cases, and Cokkinis believes that with the more general use of the diagnostic enema this percentage would be considerably increased.

Distention occurs, early or late, in about one-half of the cases and may involve only the upper or lower half of the abdomen.

The temperature is generally normal or subnormal, being at first the temperature of shock, but later when gangrene and peritonitis set in it will, of course, rise in response to the infection. The pulse is more likely to be slightly elevated early, and will generally be weak and irregular in character in contradistinction to the full, bounding pulse of early febrile conditions. However, there may be little or no alteration in either pulse or temperature for some time, but the white blood count will nearly always give the lie to their apparent lack of response. Marked leucocytosis, averaging from 15,000 to 20,000 and often rising to 25,000 or 30,000, is one of the outstanding features of the disease; a white count out of all proportion generally to the apparent severity of the illness. Later the picture changes to the usual

complex of peritonitis with marked shock. And, finally, one of the most frightening aspects is the great speed with which many of these patients go on to death; in one of our cases the patient was dead within 3 hours of the appearance of the initial symptoms.

To repeat, sudden, severe abdominal pain, accompanied possibly by vomiting, with diarrhea or sudden constipation, shock, subnormal temperature, a high leucocytosis, possibly with blood in the stools, and with diligent search presenting a predisposing cause, should always make the clinician include thrombosis of the mesenteric vessels among his possible diagnoses. We use the word vessels here advisedly because, after all, a differential diagnosis between occlusion of the veins and arteries is highly speculative in the majority of cases.

PROGNOSIS AND TREATMENT

Of prognosis and treatment, relatively little need be said. The figures in Table VIII speak for themselves. If the disease is diagnosed early, and operation performed with resection of the involved bowel and its mesentery, the prognosis is relatively good but falls rapidly with every hour of delay until, after 24 hours of acute symptoms, the outlook becomes extremely bad. We do not say hopeless, for such an attitude, which was that adopted in the first case which came to our attention, results usually in nothing being attempted for the benefit of the patient, thus depriving him of whatever chances of recovery he may have had. In 5 cases in our series which recovered, the patient is definitely described as being in "shock" or in "very bad condition" at the time of operation, further facts which incline us to the belief that when dealing with a condition which is known to be almost uniformly fatal without operative interference, the only course is to give the patient whatever chance an operation may offer.

Considerable controversy raged at one time around what type of operation should be performed, but the consensus today seems to be that so long as the infarcted bowel and its obstructed blood supply are removed, it makes very little difference what type of procedure is used. Anastomosis done at the time or later seems to give equally good results, and the surgeon's judgment of the individual case must suffice. Hartglass mentions the one exception to resection which we believe to be justified when he refers to a rare type of case in which the mesentery is infarcted but the bowel is already getting adequate circulation from collateral sources; he urges careful investigation of every case in which the bowel looks to be in good condition, because in this type of case only the necrotic mesentery need be resected. Obviously great care must be exercised not only to be sure that the case is not an ordinary one in too early a stage to show bowel changes and that the bowel is really receiving circulation from other sources, but also care must be used in resecting the mesentery not to interfere with those channels.

The extent of the infarcted bowel also seems to be of secondary importance, for death is reported when only a few centimeters are involved, while Wulsten reports, and quotes Doerfler as also reporting, a case in which the patient recovered after resection of all but a few centimeters of upper jejunum and terminal ileum. The important thing is not how much bowel is removed, but how necrotic it is and how long the patient has had to endure both the obstruction and the presence of toxic necrotic tissue. Parker emphasizes very strongly that the surgeon must not be niggardly in the amount he resects, but must go far enough into apparently healthy bowel and mesentery to be sure that he is well beyond any region of incipient involvement, a task often requiring no little courage.

CASE REPORTS

CASE 1. P. R., white male, age 67 years, was admitted under the care of Drs. F. Gorham, Brigham, and F. H. Lahey to the New England Deaconess Hospital September 14, 1928, complaining of diarrhea and pain in region of the anus. For 1 week, 3 weeks before admission, he had had severe diarrhea, with 10 to 12 movements daily. For the next 3 or 4 days he was completely constipated and then had 3 to 4 movements a day, his usual number. Ten days before admission one movement consisted of pure, fresh blood. Two days before admission he had definite chills and for the past month had been somewhat feverish, with a highest recorded temperature of 102.4 degrees F. Physical examination showed a well developed, obese, white male. The large, fatty abdomen was slightly distended but not tender. Proctoscopic examination revealed bloody stools and a negative mucosa. X-ray examination with the aid of barium enema and a gastro-intestinal series proved negative. The urine showed a few red blood cells and many white blood cells. There was a slight amount of both sugar and albumin. The white blood count was 22,500, temperature 100 degrees F., pulse 110, respiration 22. All stools contained blood. Wassermann reaction was negative. On the fourth day temperature rose to 101.6 degrees F. and patient became jaundiced. He had no definite pain but marked weakness and sweating, with vague abdominal distress. Subsequently the chest showed evidence of consolidation. Pulse rose to 180 and patient died 18 days after admission. Chief anatomical diagnoses: thrombosis of portal and mesenteric veins; syphilitic cirrhosis of liver.

CASE 2. S. W., white male, age 51 years, was admitted under the care of Dr. F. H. Lahey to the New England Deaconess Hospital about noon of July 28, 1932, as an emergency case. He had had severe abdominal pain for about 6 days, sudden in onset, originating high in the epigastrium, and cramping in character. The pain had continued without much change in intensity or location. Constipation had been almost complete since the onset of the pain, the patient having had only one bowel movement

and passing only a small amount of gas. He had not vomited until the day before admission and then only once. On the day of admission he had developed considerable pain in the left lower quadrant.

The past history showed that he had never been constipated before, but had had occasional attacks of severe epigastric pain over a period of about 6 months. These attacks had not been related to meals. Last attack had been on July 4, and had equaled the present attack in severity but had cleared up spontaneously in a short time.

Physical examination revealed a well developed and well nourished man, exhausted and dyspneic on movement. The skin was cold and clammy, and the pulse fast and thready. His abdomen was markedly distended, markedly tender over the epigastrium and left lower quadrant and slightly tender over entire left side, but without rigidity. Rectal examination revealed a tender mass high on the left side of the pelvis. Blood pressure was 100/80, white blood cells, 21,000, blood sugar, 313 milligrams per 100 cubic centimeters; urinary sugar, 5 per cent; temperature, 96 degrees F., pulse, 120, respiration, 30.

The discharge note states, "He was obviously inoperable in his present condition." He was given intravenous 10 per cent glucose balanced by insulin and later placed on a continuous venoclysis of 5 per cent glucose balanced by insulin. He became rapidly worse, however; his temperature, pulse, and respirations rose to 104 degrees F., 120, and 35, respectively, and he died on the morning of July 29, 1932. The pathological findings have already been considered. Chief anatomical diagnosis: thromboses of superior mesenteric vein and its tributaries.

CASE REPORTS FROM LITERATURE

1. Coston. White male, aged 62 years. On the "24th" patient took calomel and sal hepatica. He had loose movements next morning. At 5 p.m. he had a "tarry" stool, great pain in abdomen, and collapsed. He was seen at 8 p.m. of "the 26th". He had had obstipation for 24 hours; vomiting had been bilious at first and later fecal. Temperature was 101.5 degrees; pulse, 130. Pain was most intense at and below the umbilicus. He was operated upon and 5 feet of small intestine was resected. The veins were thrombosed. Patient died in 12 hours.

2. Mason. White female, aged 35 years, was admitted to the hospital for an interval appendix. Thirty hours later she developed signs of obstruction and operation after another 24 hours showed infarction of the ileum for a distance of 4 feet. The veins from the appendiceal stump were found to be thrombosed at autopsy.

3. Mason. White female, aged 35 years. Patient had had a pelvic laparotomy 1 year before. Following this she had a sense of fullness after meals. Two weeks before admission this became much worse. On the morning of May 17 she had a small bowel movement. In the evening she was seized with sudden cramps, took some purges and enemas, and rapidly became worse. She was operated upon 20 hours after onset of pain. At this time, the abdomen was distended and tender over the lower half, and the patient was experiencing severe nausea and griping pain. At operation an adhesion was found pulling on the under side of the mesentery, causing a sharp kink in the veins. Sixty-five inches was resected and the veins were found to be thrombosed. Patient made a complete recovery.

4. Smith, J. F. White male, aged 54 years, was seized with sudden severe pain and for next 2 or 3 days vomited dark brown material and had dark colored, watery stools. He was seen after 3 days and had some abdominal rigidity, distention and dullness in the flanks. Temperature was 100 degrees; pulse, 110. At operation a large amount of bloody fluid was found in the abdominal cavity, but there was no obvious occlusion. The process was found to involve 3 or 4 feet of the lower small bowel, and several veins were thrombosed. Patient died immediately after operation.

5. Mitchell. White female, aged 20 years. Patient was a healthy, athletic girl. She was seen April 13, 1921. The past history was irrelevant. She had been mountain climbing the day before and shopping that morning. She was seized with sudden, violent epigastric pain at 2 p.m. The pain became worse and vomiting set in. The pain and nausea continued through the night. Temperature was 98.2 degrees; pulse, 72. No tenderness or rigidity was noted. Enema gave normal movement and much relief. The next morning the abdomen was a trifle full but not tender. A mass was felt above the pubis. Pulse rose to 120. She was operated upon at 3 p.m. The abdomen contained a large amount of bloody fluid. One coil of ileum 18 inches from the ileocecal valve was infarcted along the corresponding mesentery. No pulsation was felt in the vessels. The line of demarcation was sharp at both ends. Resection and lateral anastomosis were done. Patient recovered.

6. Wulsten. White male, aged 64 years. There had been "venous spasm" with inflammation and ulceration for 16 years; thrombophlebitis of left leg, 1½ years. Four days before admission he was seized with sudden pain in the abdomen. He did not vomit but there was slight distention. The belly was tense and showed diffuse tenderness—worse below the umbilicus. The last bowel movement was 2 days before. There were no peristaltic sounds. Temperature was 35.8 degrees C.; pulse, 80. Diagnosis: mesenteric thrombosis, secondary to appendicitis. General peritonitis with bloody exudate was found at operation; gut was distended, dark red, and covered with fibrin. The entire jejunum and ileum were resected and side-to-side anastomosis was done. The result was ultimate recovery and survival with pancreatic enzymes by mouth. A segment of the small bowel, about 3.5 meters long, showed hemorrhagic infarction and venous thrombosis.

7. Jacobi. Case 1. White male, aged 59 years. The past and family history was negative. Patient suffered an injury to the right leg, in February, 1922. The wound healed, but in November, 1923, thrombophlebitis of the right leg appeared. He had a relapse with fever, April 25. Intestinal symptoms were noted June 6, with diarrhea and later dysentery. Death occurred on July 1, with symptoms of peritonitis and intestinal obstruction.

Autopsy: clinical diagnosis—sigmoid carcinoma.

The abdomen contained one-half liter of thick blood. There were hemorrhagic infarcts of the transverse colon, the tip of the mesentery, and the intestine. A loop of gut was stuck together with pus pockets between. There were many adhesions. Gray green but glistening discoloration of the ascending colon and small and large intestine was noted. Thrombi noted in the middle veins of the mesentery were adherent to the walls; thrombi were also noted in the mesocolon of the transverse and sigmoid colons. The middle mesenteric and superior hemorrhoidal veins were thrombosed. The splenic vein was free. The right femoral and popliteal veins were obliterated.

Anatomical diagnosis: localized peritonitis with bleeding in abdomen following hemorrhagic infarct of small and large intestines. Thrombosis of many mesenteric vessels of the small and large intestines. Increase of red blood cells, total blood volume with splenomegaly. Red bone marrow. Old healed inflammatory thrombosis of veins of right leg.

8. Jacobi. Case 2. White male, aged 50 years. Patient had always been healthy. Fourteen days before admission, he was suddenly seized with stoppage of feces and urine, with pain in the left upper quadrant. He became progressively worse, with vomiting, wasting, and livid coloring

The pulse was imperceptible, breathing spasmodic, belly distended, tympanitic above and dull at sides. Blood was present in the rectum. There was general abdominal tenderness and no peristaltic sound, no rigidity. Patient died February 21, 1927, 15 minutes after arriving at clinic.

Autopsy: clinical diagnosis—ileus or perforation.

Eight hundred cubic centimeters of bloody fluid was noted in the abdomen. The upper third of the small intestine was blood soaked and swollen. The spleen was large, adherent, the cut surface red, bulging, without normal architecture, and contained an infarct the size of a grain of corn. The splenic vein, portal vein, and the veins of the mesentery and omentum were thrombosed. The arteries were free. The intestinal wall and mucous membranes were swollen, blood soaked, and sloughing. The marrow of the femur was red and solid.

Diagnosis: polycythemia rubra, splenomegaly with infarct, thrombosis of mesenteric veins, and hepatic veins, hemorrhagic ascites.

9. Obadalek. White male, aged 12½ years. The past history was negative. Seven days before admission he was seized with severe abdominal pain and chills. He improved after 3 days and went to school. The day of admission he was seized again while eating, by severe pain, chills, and vomiting. The last stool and passage of gas was 2 days before admission. Physical examination revealed abdominal facies; tongue, dry; pulse, weak. The abdomen was distended and tympanitic, worse above the umbilicus. Board-like spasm and diffuse tenderness were noted in both lower quadrants, worse on right. There was a shifting dullness in the flanks. Temperature was 38.8 degrees C.; white blood cells, 9800; polymorphonuclears, 85 per cent; no eosinophils. Diagnosis: appendiceal peritonitis. At operation 500 cubic centimeters of free fluid was found in the abdomen—serosanguineous, with clots. The jejunum was distended, dark blue in color, and the serosa was studded with petechiæ. The mesentery of this part of the gut was 1 centimeter thick, edematous, pitted on pressure, and was shot through with hemorrhages which merged into a general hematoma at the base of the mesentery. The mesenteric lymph nodes were palpable. Transition was sudden. The contents of the bowel were seen through the wall as bloody fluid, and masses of Ascaris lumbricoides were seen in all parts of the bowel. Appendectomy was done. Patient was discharged well after 18 days.

10. Winters and Anderson. White male, aged 35 years. Patient had been in the hospital for hemiplegia. He was seen at 9 a.m. when he was feeling ill, respirations were faint, and shallow, his expression anxious, and his skin moist. Pain was diffuse and the abdomen was slightly distended and rigid. The temperature was 100.6 degrees; pulse, 130 and weak. He was seen again at 12:15 p.m. *in extremis*. The pulse was 150 and irregular. Respiration was 40. The skin was blue, perspiring, and cold. The abdomen was markedly distended. He vomited "coffee grounds" vomitus. The bowels had been moving about every hour, with bloody movements. He died in a few minutes.

Autopsy: The intestines were tense, dark red, and the belly contained a large amount of bloody fluid. The omentum was adherent to the body walls and contained one hemorrhagic area. The transverse and descending colons were both negative. All mesenteric veins and transverse gastro-epiploic veins contained clotted blood, and the terminal portion of the mesenteric vein was a firm, organized thrombus.

11. Kratzeisen. White, ? sex, ? age. Extirpation of the spleen was done January 18. May 20, patient was seized with sudden pain in the back, worse on the left. By May 28 patient had definite ascites. May 30, looked bad, and again had severe cramping pain; no vomiting, no peristalsis, ascites worse. June 11, exitus. Patient vomited once, just before death. Clinically had had polycythemia vera.

Autopsy: The portal vein was small and studded with thrombi. The middle loops of the bowel were fully necrotic, showed hemorrhagic infarction of the mucosa and muscle, and the veins were thick walled and plugged with thrombi. The upper loops showed punctate focal necroses. The large bowel was intact.

12. Lommel (cited by Kratzeisen). White male, aged 42 years. Patient had had intestinal colic and bloody stools 2 years before death. Polycythemia and splenic tumor were present. He died of "embolus of superior mesenteric vein" and infarction of the bowel.

13. Loeb (cited by Kratzeisen). White female, aged 61 years. Patient was operated upon for a strangulated ileus but was found to have thrombosis of the portal vein and ileocolic vein at post mortem.

14. Brie (cited by Kratzeisen). White male, aged 42 years. Illness had been diagnosed as acute yellow atrophy of the liver. Autopsy showed portal thrombosis and infarct of transverse colon, no ascites.

15. Smith, W. White female, aged 28 years, was operated upon for an interval appendix. After operation, the abdomen became distended, she vomited, and was extremely constipated. Temperature rose, the abdomen became silent, and obvious peritonitis set in.

Autopsy: Thrombus of "ileocolic vein," with gangrene of portion of the ileum.

16. Smith, W. White female, aged 32 years. Patient had had a hysterectomy and appendectomy 4 months before. The onset was acute, with nausea, vomiting, and paroxysmal pain continuously. Temperature was 97 degrees; pulse, 64; respiration, 30. The next day enemas yielded blood. Patient lay on her back or side, knees flexed, and she was in great pain. The abdomen was distended and tympanitic, with definite rigidity of the lower quadrants. White blood cells numbered 20,400; polymorphonuclears, 85 per cent; urine, 1 per cent indican. Temperature was 99.2 degrees; pulse, 76; respiration, 20. On the third day there was more tympany, less peristalsis, and the lower abdomen was rigid and tender. The cervix was movable and not tender. Enema brought pure blood. The pulse was 100. At operation the peritoneum was found to be dark and free blood was present. Fifteen inches of ileum was dark and lustreless and the mesentery was thick and edematous. The margins of the lesion were sharp. No bands or adhesions were noted. The vessels were thrombosed for an undetermined distance. The loop was withdrawn, excised, and the ends of the ileum were sutured to the abdomen. Anastomosis was done 4 weeks later; patient recovered.

17. Lang. White female, aged 60 years. Hysterectomy had been done 2 years before. Three months before she had had a fall followed by nagging pain in the back. She was treated by a chiropractor. At last visit, she told him she was constipated and he pommeled her abdomen severely. On the way home she developed severe pain and nausea. She went to bed, applied heat, vomited a laxative, and took an ineffectual enema. She became distended and faint and dizzy. She called a doctor who diagnosed acute small bowel obstruction. Patient refused operation until next afternoon, during which time she had constant vomiting, developed tenderness, distention, and a weak pulse. On admission she had marked leucocytosis. No blood was present in the stools. At operation, considerable serosanguineous fluid was found as well as a few adhesions of the omentum to the anterior belly wall. In the lower ileum, an area 8 inches long, dark purple, sausage-like in consistency, and covered with "bloody lymph" was noted. The

mesentery was swollen and edematous. The vessels were stiff and cord-like from the involved area to the root of the mesentery. A resection of 14 inches of the bowel with its mesentery and a lateral anastomosis and ileostomy at the higher level were done. Patient recovered and was well 7 months later. Pathologist's report: The specimen consisted of 14 inches of the bowel which was deeply congested with mesentery reddish purple. When the bowel was opened, the mucosa and walls appeared to be deeply congested, of deep purple color, and section showed practically all vessels with evidence of thrombosis.

18. Report at Vereinigung mitteldeutscher Chirurgen. White male, aged 67 years. "Pneumoniken." Patient presented a palpable tumor as big as a child's head below the right costal margin. Under local anesthesia about 1.2 meters of small intestine was resected. Multiple thrombi were found in the main branches of the superior mesenteric vein. Patient died after 24 hours.

19. Warnshuis. White male, aged 60 years. The past and family history was essentially negative. Patient was suddenly seized with generalized abdominal pain and vomiting. The vomitus was brown in color. The pain was chiefly in the midline, about 2 inches below the umbilicus and toward the left lower quadrant. The bowels were completely constipated. He took Epsom salts without relief. The abdomen was moderately rigid; marked tenderness was noted below the umbilicus and in the left lower quadrant. Peristalsis was visible. White blood cells numbered 27,800; polymorphonuclears, 98 per cent. At operation mesenteric thrombosis of jejunum and ileus was found, with considerable free fluid in the abdominal cavity. About 2 feet of bowel was involved. Resection with lateral anastomosis was done. Convalescence was stormy but patient finally recovered. Pathologist's report: The specimen was a piece of intestine 32 centimeters long, hemorrhagic, discolored, swollen, and very friable, with about 1 centimeter of mesentery. The lumen was filled with blood. Microscopically the wall was edematous, filled with extravasated blood and leucocytes. The mucosa was greatly swollen and hemorrhagic. The epithelium was destroyed. Some vessels were thrombosed, others clear. Sections through the mesentery showed some thrombosis, and some veins with acute phlebitis. Diagnosis: acute phlebitis of the mesenteric veins, thrombosis, hemorrhage in intestinal wall, no gangrene.

20. McClanahan. White male, aged 4 months. October 24, bowel movements were less than normal; enema clear. Next day child was apathetic, listless, and had no bowel movement. Castor oil and second enema gave small amount of bright blood. He vomited that night. October 26, he was brought to the hospital, vomiting. The abdomen was slightly distended, with no palpable masses. Temperature was 101 degrees F. A large high enema returned clear. The temperature rose to 103 degrees overnight and symptoms became generally much worse. At operation a small amount of dark red fluid was found. The distal ileum for 15 inches was flaccid, doughy, collapsed, and blue black in color. The mesentery appeared the same near the base. The belly was closed. Diagnosis: thrombosis of mesentery. Patient died next day. No autopsy was performed.

21. Rabinovitz. White female, aged 42 years. Periods had become irregular and profuse for last 3 months. September 26, she had severe abdominal cramps, localized in the epigastrium and radiating to the lumbar regions. After 24 hours pain was less severe but pressure sensation was present in the hypogastrium. Temperature was 99 degrees; pulse, 92; white blood cells, 12,400; polymorphonuclears, 79 per cent. The abdomen was enlarged and a solid tumor mass about the size of a 7 months' gestation was felt in the pelvis. Panhysterectomy was done on September 28. She vomited next day. Temperature was 99–100 degrees; pulse, 96. The next day temperature and pulse were the same but vomiting was more frequent. October 1 the condition remained the same. The bowels moved with enema. No rigidity or distention was present. There was slight pain in the lower part of the abdomen. By October 3, pulse had increased to 118, vomiting was almost incessant and with fecal odor, but the abdomen was still soft and not tender. At operation, no free fluid was found in the abdominal cavity. In the left side of the cavity was noted a coil of small intestine about 9 inches long, purplish blue, distended to about twice normal size. The corresponding mesentery was edematous, hard, and indurated. The abdomen was closed and the patient died in 4 hours.

22. Smith, W. White female, aged 28 years. As she had symptoms of chronic appendicitis, appendectomy was done. After operation patient vomited slightly, the abdomen became distended, and complete constipation set in; temperature rose, and the patient died. Autopsy revealed a thrombus in the "ileocolic" vein and gangrene of part of the ileum.

23. Frank, L. White male, aged 8 years. Patient suffered a sudden onset of abdominal cramps in morning, rapidly became moribund, and died. Autopsy: Gangrene of entire cecum, terminal ileum, ascending colon, and transverse colon as far as visible. The small intestine and appendix were negative. There was a large amount of bloody fluid in the abdominal cavity. A Meckel's diverticulum was present. Cause of death: peritonitis from mesenteric thrombosis.

24. Mason, J. M. White female, aged 35 years. She had had a suspension, right salpingo-oophorectomy, and appendectomy done 10 months before. She had a feeling of fullness after meals. Patient was suddenly seized with pain, nausea, vomiting, distention. Operation revealed an adhesion from the stump of the right broad ligament to the under surface of the mesentery. The intestine was dusky, necrotic, and showed no sharp line of demarcation below, though sharp above. Fifteen inches of ileum was removed. Recovery.

25. Parker. White female, aged 40 years. Patient complained of chronic constipation for 2 days. The condition had become bad 7 days before and the last movement had contained hard, tarry lumps. On the afternoon of admission she was seized with severe pain in the left lower quadrant, later becoming generalized. The pain was sharp and distressing. She vomited three or four times. Patient was not in shock. She showed general abdominal tenderness and slight rigidity. Operation: A piece of bowel 9 inches long was removed along with a piece of mesentery. Death occurred in 24 hours. At autopsy the abdomen was found to contain 500 cubic centimeters of bloody fluid. The bowel was discolored from anastomosis to within 12 inches of the ileocecal valve. Thrombosis was found at junction of the splenic and superior mesenteric veins, extending almost to the spleen, into the portal vein, and down the superior mesenteric vein. The liver showed thrombi in the portal radicles. Microscopic examination: The pancreatic vessels contained antemortem thrombi; and part of the tissue degenerate; the liver, areas of degeneration, irregular in shape with some vessels thrombosed. Diagnosis: Thrombosis of splenic mesenteric, and portal veins. Pressure by head of pancreas on junction of the splenic and mesenteric veins.

26. Wilson. White female, aged 35 years. Five days before the patient had been seized with pain which was colic-like at first but later became continuous and severe. She vomited several times and felt better. Three days after onset, the pain became much worse and the vomiting more frequent. There had been no bowel movement for 2

days before admission, in spite of enemas. The abdomen was distended and slightly tender below and to the right of the umbilicus. An indefinite tumor mass was palpable in this region. Tympany and shifting dullness were present. Operation: bloody fluid was found in the peritoneal cavity. The small bowel was blue and lustreless from "upper part" to within a few feet of the ileocecal valve. There was no sharp line of demarcation. The arteries were engorged and the veins blue and cyanotic. A collection of firm clots formed a mass in the upper portion of the mesentery. The abdomen was closed; it was felt that it would be too much to resect. The vessels looked as if the inferior mesenteric vein was taking over the function of the superior vein. Convalescence was uneventful.

27. Ross. White male, aged 46 years. Patient had had two attacks: one 6 months and the other 1 year before. Two days before admission he had developed pain in the right lower quadrant, had had no bowel movements and the abdomen had become distended. A palpable mass was felt in the right lower quadrant. Operation was done 4 days after admission. The bowel around the cecum was gangrenous. There was no mechanical obstruction. Autopsy showed through the operative wound, thrombosis of veins from the ascending colon.

28. Ross. White male, aged 52 years. Patient gave a 7 day history of pain, vomiting, and constipation. He had not been operated upon. Patient died 24 hours later. "Mesenteric thrombosis with gangrene of proximal 4 to 6 feet of ileum."

29. Laws. White male, aged 10 years. Patient had had acute abdominal pain followed by vomiting. A course of calomel was followed by passage of a large quantity of blood; a few hours later two small bloody stools. The severe colic-like pains continued with vomiting. Four days later the abdomen was distended moderately, rigid, tender, especially below and to the right of the umbilicus. Feces revealed nothing but the presence of old blood. He was completely constipated and had complained for several years of abdominal pains in the mornings. White blood count was 17,600; polymorphonuclears 86 per cent. At operation, considerable bloody fluid was found in the abdominal cavity. Two feet of small intestine was found to be distended, edematous, and purple in color. The line of demarcation was sharp at both ends. A kink was found which was thought to be secondary to other pathological conditions. The mesentery was studded with hard lymph nodes of various sizes, thought to be tuberculous nodes. The mesenteric veins corresponding to the damaged segment were thrombosed. No resection was done. Patient was very ill for 2 more days and finally recovered. There was no return of the abdominal symptoms present before operation.

30. Nifong. White male, aged 26 years. The past history revealed a similar attack 4 months before, for 5 days. The present onset was sudden with vomiting. He was given castor oil, enemas, and morphine. Temperature was 97 degrees. The abdomen was rigid. Operation was done 16 hours later. A perforated appendix and "thrombosed mesentery in the lower part of the ileum" were found. The appendix was removed and 45 inches of ileum. Patient became worse, developed wound infection, distention, dark bowel protruding into the wound, and died 11 days after operation. Autopsy was not granted.

31. Nifong. White male, aged 21 years. Patient gave the usual story, with a 6 days' delay. Bloody fluid was found in the abdomen and all the intestines were discolored. Resection was done of 60 inches of the worst looking bowel and mesentery, which was "hard and thrombosed." Death occurred 5 hours after operation. No autopsy was granted.

32. Brady. Colored male, aged 51 years. Bilateral inguinal hernias had been operated upon and at apex of the right sac there was found a large abscess. The wall of the abscess was sutured to the abdominal wall through the right rectus incision. Patient died 4 days later. Autopsy: thrombosis of inferior mesenteric vein; septic thrombosis of portal vein; no intestinal changes.

33. Brady. White male, aged 49 years. Patient had had three admissions for cirrhosis and diabetes. He developed sudden low abdominal pain 4 days before admission and died 2 days later. Autopsy: thrombosis of portal and superior mesenteric veins, hemorrhagic infarction of intestine, diabetes, cirrhosis of liver.

34. Brady. White male, aged 52 years. Patient gave a history of 3 weeks of pains in the abdomen and occasional vomiting, 5 days of increased severity. Operation showed a gangrenous gut and engorged and blackened mesentery. The loop of the gut was brought out but was not resected. Enterostomy was done. Death occurred in 2 days. Necropsy: thrombosis of mesenteric veins, necrosis, and gangrene of small intestine, general fibrinopurulent peritonitis.

35. Brady. White female, aged 45 years. Patient had been on medical service with Raynaud's phlebitis, and thrombosis of the left iliac vein. She had had 10 days of pain in the lower abdomen, and 1 day of vomiting. There was marked tenderness. At operation, a mass was disclosed in the upper abdomen made up of matted loops of bowel near the point of gangrene. Thirty inches of bowel was removed and a lateral anastomosis was done. The patient recovered.

36. Brady. White female, aged 31 years. Patient had had severe back pain and vomiting for 8 days. This was replaced by epigastric pain and delirium. Red blood cells, 7,680,000; hemoglobin, 112. At operation, a coil of intestine, distended and black, was noted. No pulsation was present in the mesenteric arteries. Resection of 60 inches of the bowel and lateral anastomosis were done but patient died in 24 hours. Autopsy: polycythemia, atrophy of the liver, thrombosis of branches of portal vein with extension to mesenteric veins from stomach, intestine, and spleen, hypoplasia of bone marrow, infarction of small intestine, and acute peritonitis.

37. Brady. White female, aged 24 years. Patient gave a history of rheumatic fever and edema of ankles. She had had a miscarriage 10 days before admission. She was suffering from sudden pain and vomiting. She was admitted to the hospital after having been in irrational state for 30 hours. The white blood count was 23,000; temperature, 102 degrees. Mitral stenosis and insufficiency, rigidity and spasm of the abdomen were noted. Operation consisted in the removal of 40 inches of gangrenous mesentery and intestine. The peritoneal cavity contained considerable bloody fluid. A secondary anastomosis was done and the patient recovered. Premortem thrombi and white cells were found in the vein lumina and walls.

38. Johnson. White male, aged 55 years. The past history was negative. The present illness was sudden, with general abdominal pain. Vomiting followed 30 minutes later, along with an increase in pain. Patient had had no bowel movement since the day before. There was a board-like rigidity with marked tenderness. Temperature was 95.2 degrees; pulse, 52. There was discoloration of the abdomen as seen in an ectopic pregnancy. Operation disclosed bloody fluid in the abdomen. The mesentery, part of the jejunum, and part of the ileum, were of a dark purple color. "Mesentery was so thickened and intestine so edematous and so moist that the diagnosis was made of a thrombosis or embolism of the mesenteric veins rather than of the arteries." Four feet and 2 inches of bowel was resected, and patient made an uneventful recovery.

39. Falkenburg. White, ? age, ? sex. Patient came to the clinic with symptoms of ileus. Stools had been bloody. Operation showed thrombosis of the superior mesenteric vein with secondary gangrene of the bowel. Involved loops and corresponding mesentery were resected. Patient was discharged well.

40. Ross. White male, aged 46 years. Onset was sudden, with pain in the right lower quadrant, followed by vomiting. Purgatives gave no result. There was no fever or chills. He had had previous attacks, 6 months and 1 month before. The abdomen was distended with a tumor-like fullness in the right lower quadrant, and it showed marked tenderness and rigidity. Peristalsis was present in the upper and left lower quadrants. Rectal examination revealed marked tenderness. He was operated upon 4 days after admission to the hospital with a diagnosis of appendicitis. The bowel was found to be gangrenous, and it ruptured during operation. At autopsy the veins leading to the ascending colon were found to be thrombosed.

41. Ross. White female, aged 57 years. She had had a Gilliam suspension operation about 10 days before. After 1 week, she developed phlebitis of the left saphenous vein with extension to the iliac veins. The abdomen became distended, tympanitic, and tender, and the patient developed pain, nausea, and vomiting. The bowels moved by enema and patient recovered without further signs of obstruction. Bacillus coli was recovered from the blood stream.

42. Miller, H. A. White female, aged 17 years. Onset was sudden at 10 p.m., with cramp-like pains, chills, and faintness. She gave a past history of "bilious attacks." By 10 a.m. she had a tender, rigid abdomen; she had been vomiting since the previous evening. Temperature was 101.4 degrees, F.; pulse, 120. At operation, serosanguineous fluid was found in the belly with 46 inches of gangrenous bowel, reaching to within 4 inches of the cecum. In the center was a diverticulum 3 inches long, adherent to a loop of bowel. This had twisted and strangulated its blood supply, setting up a thrombosis, which extended into the higher vessel. Resection was done with complete recovery of the patient.

43. Addison. White female, aged 42 years. Onset was sudden with continuous pain, followed by swelling of the abdomen. She vomited once. On admission to the hospital she was pale, in state of collapse and with prominent, tender swelling of the abdomen, like a 6 months' pregnancy. There was no visible peristalsis; some lateral dullness. At operation, serosanguineous fluid was found in the abdomen. The intestine was dark and distended from within 3 inches of the cecum for a distance of about 9 to 12 feet. There was an abrupt demarcation above and below. Resection and jejunocolostomy were done. Patient was discharged well.

44. Ghose. White female, aged 54 years. Onset was sudden with severe abdominal pain referred to the right of the umbilicus. The pain let up for a while, but was followed by vomiting and complete bowel stasis. There was a letup for 3 days. She was admitted to the hospital, at which time the temperature was 97 degrees; pulse, 80; respiration, 26. The abdomen was slightly distended and she frequently vomited fecal material. Peristalsis was not visible. Enemas were without result. Operation revealed 12 inches of distended small bowel with attached mesentery deep chocolate in color. The mesentery was soft, edematous, and friable. The veins were thrombosed. Resection and lateral anastomosis was done with recovery.

45. Murray. White female, aged 14½ years. The past history was negative. The present illness began with a sudden attack of acute abdominal pain. Bowel movement had occurred earlier in the day. There was no vomiting. Temperature was normal, pulse, 140. The abdomen was tender with no distention. She was relieved within 4 hours. Twelve hours later she had a second attack, and 2 hours later, she was in collapse. She was operated upon 20 hours after onset. Operation consisted merely in drainage. Postmortem, 6 hours later, revealed 10 feet of small bowel distended and with early gangrene. At base of the mesentery was a caseous lymph node from the region of which the thrombosis spread fanwise in both arteries and veins. The bowel had a sharp line of demarcation.

46. MacLeod. Male, ? age. April 14, splenectomy had been done for pernicious anemia. Two hours after operation there had been copious hemorrhage from the mucous membrane, followed by second hemorrhage 2 hours later. Clotting time was delayed. Coagulose in full doses was given for 2 days. May 18, he suffered severe abdominal pain with a sensitive mass in the lower right quadrant. The temperature and pulse were above normal; he had slight vomiting and diarrhea. May 20, abdomen was distended, free fluid was present in the abdominal cavity, and a mass was still palpable. Vomiting was not urgent or projectile in nature. Temperature and pulse were above normal. At operation a mass consisting of a coil of small intestine, gangrenous as a result of thrombosis in a radicle of the superior mesenteric vein, was noted. Resection was done of the gangrenous intestine and sufficient living intestine to be well outside the limits of the thrombosis. Death occurred in 4 days. Postmortem revealed that the thrombosis extended into the mesenteric veins and up into the portal vein; the splenic vein was filled with recent soft thrombosis.

47. Brady. White female, aged 60 years. Patient was admitted to the hospital with auricular fibrillation and cardiac decompensation. She had a distended abdomen, but no pain. On the fifth day in the hospital she developed sudden severe pain and died in 24 hours. Postmortem examination revealed arteriosclerosis, myocarditis, cirrhosis, thrombosis of the superior mesenteric veins, and hemorrhagic infarction of the intestine.

48. Eliot. Female, aged 57 years. Patient had had 3 previous operations. She had varicose veins. A year and a half ago she had fallen striking her abdomen. After the fall she suffered occasional soreness in the lower abdomen. The onset of the present illness was sudden with acute continuous, shooting pain from right to left above the navel. The pain moved downward. Two hours later she began to vomit. The bowels had moved a few hours before the attack and afterward, with enema. There was no gas or blood. Physical examination showed that the whole belly was tender, more so in the midline; there was symmetrical rigidity of both rectus muscles; no distention; there were sounds of active peristalsis. Rectal examination was negative. Sixteen hours later, distention began and a tender mass was felt below the navel both in front and rectally. At operation, bloody fluid was found and 3 feet from the ileocecal valve was a loop of intestine 15 inches long, dark purple, and covered with fresh fibrin. There was a sharp line of demarcation. The mesentery was infiltrated and the veins contained thrombi, while arteries did not pulsate. Resection and anastomosis were done and the patient recovered.

49. Eliot. Male, aged 22 years. Several months before, patient had had similar attack, less severe, lasting 24 hours. Thirty-four hours before he had had severe sharp pain around the umbilicus, increasing in intensity; not relieved by morphia. He vomited mucus. The bowels, ordinarily constipated, moved several times, with catharsis, no blood. The temperature was 101 degrees; pulse, 144; respiration, 36. The abdomen was slightly distended, motionless, and tender, principally in the right lower quadrant. Sounds of active peristalsis were heard. Rectal tenderness was bilateral. Operation disclosed 14 inches of bowel, black in color, 2 feet from the cecum. The mesentery was black and

swollen and without pulsation. The veins did not bleed. Patient recovered after abscess in the sound, fecal fistula, and right femoral phlebitis.

50. Eliot. Male, aged 60 years. Patient had had typhoid and phlebitis years before. Two days before admission to the hospital he had had abdominal discomfort and nausea. The next day his condition was about the same. He tried indigestion remedies but became worse, with pain settling in the right lower quadrant. The bowels began moving and he passed bismuth taken during the first day. There were tenderness and rigidity on the right in the region of the umbilicus; no distention. Pulse was 120; white blood cells, 25,000; polymorphonuclears, 95 per cent. At operation, 14 inches of purple colored bowel, 10 inches from the cecum, was resected. The veins were thrombosed and had no pulsation. Twenty-four hours later, patient was in good condition but developed sudden severe pain. The abdomen was reopened and a perforation was found 6 inches from the cecum. Death occurred 8 hours later. Microscopic examination: extensive venous thrombosis.

51. Eliot. Male, aged 38 years. One hour after daily bowel movement, he was seized with general abdominal pain, dull, constant, and persistent; no nausea or vomiting. He was relieved by morphia that night. The second day, the same condition prevailed, with the addition of bloody stools. A high oil enema gave dark blood. On the third day, the pain was less; temperature, 100; pulse, 80. Patient looked well. There were tenderness and rigidity in the right lower quadrant. Rectal tenderness was bilateral. There was no palpable tumor. Operation disclosed bloody fluid; 2 feet from the cecum, 20 inches of necrotic bowel with sharp demarcation. The veins were thrombosed and had no pulsation. Resection of 32 inches of bowel, anastomosis, recovery.

52. Weil (cited by Eliot). Female, aged 52 years. Obstipation had been noted for 3 years. Present illness began with sudden abdominal pain, general; and vomiting. Belly was soft with tenderness and resistance over the bladder and the left lower quadrant. There was slight distention. Pelvic examination showed sensitive elongate tumor. Pulse was 90; temperature, 97.6 degrees. Operation disclosed bloody fluid in the abdomen, 2 feet of bluish red intestine with sharp line of demarcation; mesentery edematous; and veins thrombosed. Resection and ileocolostomy resulted in recovery.

53. Davis (cited by Eliot). White female, 45 years of age. Five years before, patient had a similar attack for 2 or 3 days and again 2 years before, both of which cleared up. "For days" she had had general mild abdominal pain. Patient menstruated and pain became worse and paroxysmal in type. The pulse and temperature were subnormal. Patient was in mild shock but operation was delayed. The next day she vomited, and had tenderness and slight rigidity. Enema brought bloody fluid. The abdomen was distended, fluid was felt in the flanks, and peristalsis was visible. Operation was done about 40 hours after onset. Bloody fluid was found in the abdomen. There were 18 inches of small bowel, rigid and deep purple in color. There was a sharp margin above and below. The mesentery was thickened and the vessel thrombosed. Resection was done with secondary anastomosis. Patient was discharged well

54. Mole. ? race, male, aged 42 years. Patient was admitted to the hospital during a cholera epidemic. Onset was 24 hours before, with vomiting, watery diarrhea, and cramps in the legs. He was pulseless and lived only 24 hours. The abdomen became distended shortly before death. Autopsy showed the lower part of the small bowel distended; 3 feet at lower end dark chocolate color, with here and there thin exudate on the surface; most of the peritoneum was shiny; mesenteric lymph nodes were enlarged. Some mesenteric veins were thrombosed from the foot of the mesentery to the bowel wall; others were free. The bowel contents were bloody rather than rice water in appearance. Microscopically the mucosa was markedly thickened and filled with congested blood vessels and hemorrhages. Many foci of necrosis were noted in the mucosa and wall. Peyer's patches were markedly congested.

55. West. White female, aged 20 years. Patient was admitted to the hospital giving a history of severe abdominal pain for 3 days, increasing in severity and associated with vomiting. The abdomen was distended and tender, and patient was unable to co-operate. On deep, forcible palpation, a mass was felt to the left of the spinal column. Pulse was 120; temperature 101.5 degrees. Operation was done 8 hours later. All of the small intestine appeared far advanced toward gangrene. The superior mesenteric vessels were constricted by a band passing across the abdominal cavity just above the umbilicus, which proved to be the mesentery of the cecum which had revolved toward the left. The appendix was inflamed. The adhesions were freed, the appendix was removed, and the cecum revolved and fixed. The bowel began to regain color and was not resected. Patient recovered. Double pyosalpinx was not operated upon.

56. Michael. White female, aged "young." Young woman had previously been well except for a miscarriage 4 months before. For 1 month she had had occasional vomiting and suddenly developed intense, paroxysmal umbilical pain. The spleen was enlarged, and the patient showed an anemia of 38 per cent. At operation, 3 meters of the small bowel, edematous and discolored along with the corresponding mesentery were noted and resected. The veins were found to be thrombosed. She recovered. One month after operation she developed femoral phlebitis which soon subsided.

57. Geppert. White male, aged 40 years. Three days before he had had a sudden attack of severe colic-like pain in the upper abdomen; no fever, diarrhea, obstipation, or vomiting. The last bowel movement was 30 hours before admission on the third day. There was some tenderness in the left upper quadrant, with slight rigidity. No free fluid or peritonitis was found. After a short time patient had an exacerbation of symptoms, vomited bloody fluid, went into collapse, and died. The condition was diagnosed clinically as mesenteric thrombosis. Autopsy revealed 500 cubic centimeters of serosanguineous fluid in the lesser peritoneal cavity. From the beginning of the jejunum for 1 meter, the bowel was dark blue red in color and the mesentery thickened toward the portal region. The mesenteric vessel contained thrombi with dark center and pale margin. The jejunal stem of the superior mesenteric vein was occluded throughout by dark red, fresh thrombus. The wall of the vein was three times normal thickness as was true of the splenic and portal veins. The oldest thrombus 6 centimeters long was found near the splenic portal junction. The last 4 centimeters of the portal stem was clear. The stomach mucosa was hemorrhagic and doughy. Microscopic examination confirmed the gross. The intima of the veins was thickened and the elastica markedly increased. Many infarcts were found in the liver and were thought to represent old and recent phlebitis. Fat necrosis was found in the pancreas.

58. Bucura. White female, aged 23 years. Patient had had a normal delivery on January 6, after a pregnancy which gave symptoms of impending eclampsia but never progressed to actual convulsions. On January 16, she was suddenly seized with vomiting and cramps. She became completely constipated. The next day she was much worse and the abdomen was generally tender. At operation, the

intestines were found to be gangrenous for 12 centimeters. During operation, the process could be seen extending and the patient died 20 hours later. The mucosa of the resected bowel was intact, but the wall was gangrenous and the veins were thrombosed.

59. Miller, L. I. White female, aged 22 years. While skating, the girl fell and was kicked in the abdomen. She had a dull pain in the right lower quadrant for 10 days and then was seized with sudden severe, generalized pain. She came to the hospital 4 days later after being seen by four doctors. White blood count was 28,000. She died very shortly from shock. Autopsy revealed thrombosis of the veins of the descending colon and involvement of 25 centimeters of bowel.

60. Peyrot. White male, aged 21 years. Patient was seized with sudden, violent abdominal cramps and fecal vomiting. This lasted about 24 hours before operation. Three and one half meters of small intestine was found to be gangrenous; a cecostomy was done and the infarcted bowel was returned to the abdomen. Patient died 10 hours later. Autopsy confirmed the clinical diagnosis of thrombophlebitis of the mesentery with vascular occlusion and infarction. Five and two-tenths meters were found to be involved, starting 80 centimeters from the ligament of Treitz.

61. Skeel. White female, aged 21 years. Seven weeks postpartum, patient had had phlebitis. She got up and walked around and was seized with severe abdominal pain followed by vomiting. She died in 22 hours without operation.

62. Banke. White male, aged 47 years. Illness began as malaise without pain. Pain developed about 6 hours later, along with vomiting, distention, and shock, but without bloody or fecal vomiting. Operation consisted in resection of 435 centimeters of small intestine which was gangrenous. A slight amount of "putrid" ascites was found. Microscopic examination showed marked arteritis and thrombosis of both veins and arteries. Patient recovered.

63. De Quéme and Autefage. White male, aged 39 years. For 1 day patient had had bilious vomiting, retention of gas, and meteorism. Diagnosis: appendicitis. At operation a fetid, serosanguineous fluid was found in the abdomen. In the ileum a loop of bowel 25 centimeters from the ileocolic valve, 15 centimeters long, which was black and dilated, was noted. Twenty centimeters was resected. Grossly the mesenteric veins were thrombosed. Patient recovered.

64. Moirud. White female, aged about 50 years. Because patient could not speak French, very little history was obtained, but apparently she had had cramps and vomiting for 4 days. The abdomen was distended and tympanitic, vomitus was black, and stools were tarry. Autopsy revealed a large quantity of serosanguineous fluid. The epiploicæ were retracted and blood soaked. Two meters from the duodenum, the bowel was distended and wine red in color. The lesion was sharply defined. The mesentery was infiltrated with blood for about 10 centimeters. The lumen of the bowel was filled with mucosanguinolent fluid. Dissection of the vessels showed the arteries to be free and the veins thrombosed as far as, and into, the portal vein. The liver was cirrhotic, the gall bladder chronic. Microscopic examination revealed the liver sinusoids thrombosed and the endothelium peeled off. The arteries showed endarteritis obliterans. The mesenteric vein contained a partially organized thrombus and thick media with separation of muscle fibers. The vasa vasorum occasionally were thrombosed.

65. Desplas. White male, aged 32 years. Patient had had attacks of dysenteric enteritis, of hemorrhagic dysentery, of pain and hemorrhage, of appendicitis, and of typhlo-appendicular crises in 1917, 1918, 1922, 1923, 1924. In April, 1925, he had had severe pain medial to McBurney's point. On May 2, he had had black, bloody diarrhea. On May 7, he passed 11 "selles" of black blood and developed some fever. On May 10, he developed afebrile purpura hæmorrhagica. On May 29, he had a severe attack of colic, bloody diarrhea, had sensation of impending death, and showed profound alteration in condition. The belly was ballooned, with tenderness and spasm about the umbilicus and in the right lower quadrant. Rectal examination revealed tenderness. At operation, bloody fluid was found in the belly. Twenty centimeters from the cecum, the ileum was gangrenous and the corresponding mesentery was edematous and blood soaked. Sixty centimeters was resected and the patient finally recovered after a stormy course. Histological examination revealed massive desquamation of the mucous membrane; polymorphonuclear leucocytic infiltration with fragmentation of the muscle fibers; serosa elevated by liquid edema; adjacent zones of edema of mucosa and muscularis; thrombophlebitis of the terminal branches of the superior mesenteric veins.

66. Mathin and Alivisotos. White female, aged 64 years. Patient had had 2 days of pain in the abdomen and abundant fecal vomiting. The pulse was weak, the abdomen distended and tender. The temperature was normal. After 8 days of sickness, the symptoms ceased only to recur in another 6 days. This time she was constipated and had fever as well as fecal vomiting. Autopsy revealed the entire ileum infarcted. The mesentery showed veins thrombosed and the arteries free. No cause for the condition was determined.

67. Hartglass. White female, aged 38 years. Patient gave the usual history of sudden onset, pain, vomiting, and distention. An infarcted mesentery was found at operation, with source unknown, but the bowel itself was apparently normal. The abdomen was closed and the patient recovered.

68. Ruszinski. White male, aged 57 years. Patient had always been healthy until 4 months before admission. He developed mild cramping pain which disappeared periodically, but gave a history of bloody stools. The abdomen was found to be tense and tender, especially in the right lower quadrant, about the level of the umbilicus, with no radiation of pain or tenderness. Temperature was 37.3 degrees; pulse, 100. The tongue was coated and dry. He next developed constipation and retention of gas. A tentative diagnosis was made of bowel tumor or appendicitis. Enemas and rectal tube for 2 days gave little gas. For 2 days more he was given castor oil, had a bowel movement and felt better. Temperature became normal; "tumor disappeared." Eight days later he became worse, had distention, tenderness, and appeared very ill. At operation a cloudy exudate was found. The appendix was coated with fibrin. A sausage-like tumor was present in the right upper quadrant under the liver, and was found to be made up of loops of small bowel which measured 75 centimeters in length. No mechanical obstruction was found. The mesentery was markedly swollen, edematous, and friable. The vessels were found to be occluded. The liver was nodular and small. One meter was resected. Patient died after 1½ days. Autopsy disclosed thrombosis of the portal and mesenteric veins; hepatic cirrhosis; hemorrhagic infarct of some remaining bowel.

69. Ruszinski. White male, aged 50 years, had previously been well. He had been an excessive drinker and smoker all his life. Four days before he developed malaise, mild epigastric pain, and vomiting. The pain shifted to the right lower quadrant, he had no fever, but pulse increased moderately. The family doctor said that there was tenderness over McBurney's point and a perforation of the appen-

dix was thought of. Physical examination revealed distention, spasm, and tenderness in the right lower quadrant, less on the left. Temperature was 37.1 degrees C.; pulse, 104. He had passed gas and vomited the day before. Operation disclosed cloudy fluid in the abdomen and "secondary appendicitis." A tumor was felt which proved to be small bowel and was gangrenous. No kinking or mechanical obstruction was present. The mesentery was swollen and gray in color. Resection of 1.6 meters was done. The veins of the mesentery were found to be thrombosed. Autopsy next day revealed the portal vein stem thrombosed from a narrow point behind the pancreas down into the mesenteric vein but clear above this point; cirrhosis of mild degree; old thickening of the vein wall at the initial point of the thrombosis which was thought to represent an old canalized thrombus with new thrombosis superimposed. Infarction of the bowel had extended.

70. Hedlund. White female, aged 36 years. Patient had a thrombosis in the superior mesenteric vein and ileus. Nine and a half months previously she had had a tubal abortion with operation. Since then she had had occasional colic-like pain. On November 28, 1913, she was seized with severe pain in the entire abdomen, diffuse. Temperature was 37.4 degrees C.; pulse, 74. After several hours, the pain became less. There were occasional peristaltic sounds over the umbilicus; no distention; pelvis negative; no abdominal resistance; no flatus. At operation a resection of 4 centimeters of jejunum was done along with the adjoining mesentery. Patient died during the night. Autopsy revealed hemorrhagic infarct of intestine at site of operation and mesenteric venous thrombosis.

71. Bonnet. White female, aged 28 years. Patient was operated upon on December 20 for pelvic inflammatory disease. On August 30 of the following year she developed sudden epigastric pain, not relieved by morphine, and vomiting, not fecal. She was given castor oil, enemas, pituitrin, and olive oil per rectum, without results except some flatus. No blood or distention was found but there was slight rigidity of the muscles. She became worse, pain became rhythmic, and masses became palpable in the abdomen. Operation revealed bloody fluid in the abdomen. The bowel was infarcted as well as a V-shaped piece of mesentery within 2 feet of the cecum. A resection of 224 centimeters of ileum was done and as well an end-to-end anastomosis. Patient was in shock but recovered and left the hospital. She was well 6 months later.

72. Silhol and Bourde. White male, aged 60 years. Patient was admitted to the hospital, vomiting, with distention, and without passage of gas. He gave history of sudden onset of pain in the left flank which became worse. A palpable mass was noted in the left iliac fossa—diagnosed carcinoma of the sigmoid or volvulus of the pelvic colon. At operation, a loop of ileum, 25 centimeters long, was found, turgid and purple, in the iliac fossa. The mesentery was also involved. Resection and end-to-end anastomosis were done. Patient died 8 hours later. Pathological report: the specimen consists of 32 centimeters of resected bowel with sudden transition between normal and infarcted bowel. Confirmed venous thrombosis microscopically.

73. Cabot Case 13502. White female, aged 46 years. Patient gave a history of trouble with abdominal discomfort, nausea, and dizziness for many years, more marked during last 5 years. Three years before she had had "intestinal grippe" at which time she passed large quantities of mucus. Seven weeks before she developed soreness in the epigastrium which became worse and moved to the left lower quadrant about 1 week before admission. No respiratory symptoms or jaundice were noted. The family history was positive for carcinoma. The past history was negative except for slight hypertension and subjective symptoms. Patient walked into the ward but later was seen holding the abdomen as if in great pain. Examination was difficult because of obesity, but apparently she had a large tender liver, a movable tender mass in the left lower quadrant. Blood pressure was 140/70; white blood count 10–20000. The urine showed trace of sugar; slight trace of albumin; 15 to 20 white blood cells, and an occasional red blood cell at one examination. The stools and vomitus were guaiac positive; no free hydrochloric acid was noted. X-ray examination was negative. Temperature was 100.2 degrees; respiration, 20; pulse, 77; rising to 99. Four days later note states that patient was too ill for a barium enema. Constant vomiting and abdominal pain required morphine. July 1, 6 days after admission to the hospital, she was operated upon. The abdomen was found to contain much fluid. Thrombosis of the superior mesenteric vein branches, with gangrene of the intestines was noted; also thickening of the mesentery of the transverse colon. The bowel was resected and lateral anastomosis was done. Patient died the next day. Pathological report showed: carcinoma of the stomach with two ulcer craters. Attached to the stomach carcinoma was a large tumor of the mesentery and transverse colon which, by pressure and direct growth around the vessels, caused thrombosis of both veins and arteries.

SUMMARY

Two new cases of intestinal obstruction caused by thrombosis of the mesenteric veins are presented along with 73 other cases collected from the literature and a general review of the literature from 1913 to 1933.

The pathological process is analyzed and an explanation given of the development of obstruction and hemorrhagic infarction following either arterial or venous occlusion.

A list of some of the more common etiological factors and predisposing causes is presented, with the conclusion that septic abdominal processes and cirrhosis of the liver are of the greatest importance.

A statistical analysis of several series of cases reveals the general incidence of the disease to be from 0.003 per cent to 0.007 per cent, and also that there has been a great improvement in the last few years, both in diagnosis and the results of treatment.

No definite symptom complex can be discovered to set the disease apart as a clinical entity, but rather it is classed as a fairly characteristic type of intestinal obstruction with diagnostic possibilities of about 60 per cent.

Treatment is limited to exploration and resection of infarcted bowel and mesentery, with a good prognosis in the cases operated upon during the first 12 hours of acute symptoms and an extremely bad prognosis after 48 hours.

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EDITORIALS

SURGERY, GYNECOLOGY AND OBSTETRICS

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JULY, 1935

THE SO CALLED LIVER DEATH SYNDROME IN SURGERY

CHARLES GORDON HEYD was the first to point out the significance of the so called liver deaths which sometimes follow biliary surgery and which are not to be explained by the usual factors of shock, hemorrhage, embolism, infection, and respiratory complications. Such cases, it is now recognized, fall into two distinct groups. In the first death occurs promptly after operation; hyperpyrexia is the outstanding symptom and degenerative changes in the liver are the only notable autopsy finding. In the second group death is deferred for 10 to 14 days, or even longer, uremic symptoms predominate, and autopsy reveals the liver changes just described, plus similar degenerative changes in the convoluted tubules of the kidneys. For these cases no universally applicable explanation has yet been advanced.

As the interest in this type of death has increased, there has been an increasing feeling that the syndrome is not confined to biliary surgery, but occurs, and not infrequently, in other postoperative conditions. Heyd, in his original communication, mentioned that it might occur in both pancreatic and gastrointestinal surgery. Furtwaengler, Stanton, and Helwig and Orr observed it in cases of liver trauma, and the last named authors also noted it as a late complication of mammary carcinoma. LeNoir noted it after surgery for gastric ulcer, and Connell, who in 1931 had stated that the syndrome was never apparent except after biliary surgery, withdrew the observation in 1934, and stated that he had since identified it after operations for ovarian cyst, uterine fibroids, interval appendicitis, and ventral hernia. Heuer, who has never seen it after biliary surgery, observed it after a splenectomy for supposed Banti's disease. The 26 cases of postoperative heat stroke collected by Cutting, only a few of which followed biliary surgery, seem likely, in the light of our present knowledge, to fall into the same category.

In a study of the records of the New Orleans Charity Hospital for the last 7½ years, we have been able to locate 23 liver deaths after gall-bladder surgery,[1] this being the largest single group reported in the literature to date, as well as 5 cases of pancreatitis and 6 cases of liver trauma which clearly fit Heyd's original classification. Furthermore, in a series of casually selected recent autopsies comprising burns, intestinal obstruction, and thyroid disease, we were able to find case after case in which there was evident a striking parallelism with the deaths which occurred after surgery for biliary and pancreatic disease and after liver trauma. In most instances, when the clin-

[1] Boyce, F. F., and McFetridge, E. M. A clinical and experimental study of the so called "liver death." Arch. Surg., in press.

ical course was typical the postmortem findings were also typical, i.e., necrotic changes in the liver, with or without similar changes in the convoluted tubules of the kidneys, depending upon how long the patient lived after operation had been performed or after injury had been sustained.

Our own hypothesis, which is based upon a study of the cases just listed and upon a series of personal experiments,[1] is that the same syndrome is apparent and the same underlying factors are operative in all of these conditions, as well as in many others, perhaps, in which it has not yet been recognized. In such cases, we postulate, the underlying factor is some degree of liver damage which is not incompatible with the strain of normal life but which is incompatible with the added strain of disease or of trauma. When this strain is superimposed upon the existing hepatic disability, the damaged liver cells, failing in their function, release into the circulation some potent toxic substance. This substance, circulating in the blood, is excreted by the kidneys through the convoluted tubules, which, unfitted by nature for such a load, break under it. It seems not unreasonable to assume, further, that the liver kidney syndrome is a single pathological process, rapid hyperpyrexia deaths, in which only liver changes are apparent at autopsy, being simply the first stage of the process which, if it continues, later terminates in the uremic type of death, with renal as well as hepatic changes apparent at autopsy.

FREDERICK FITZHERBERT BOYCE.

EARLY AMERICAN MEDICAL SCHOOLS

THE COLLEGE OF MEDICINE OF THE OHIO STATE UNIVERSITY

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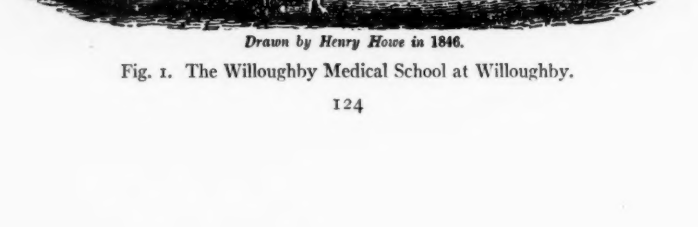
Sometime Assistant Professor of Pathology, Lecturer on Diseases Due to Allergy, The Ohio State University

IN 1796, the Connecticut Land Company bought three million acres of land in the Connecticut Western Reserve and became the dominant influence in northeastern Ohio, sending out a great many settlers from New England.

On March 3, 1834, the Ohio Legislature passed two bills of great significance to the Ohio State University which was destined to be established in Columbus by the same legislative body forty-two years later: the first was a charter for the city of Columbus which since its founding in 1816 had been a borough; the second was a charter for the Willoughby University of Lake Erie to be located at Chagrin, Ohio. This charter gave the power "to grant degrees in the Arts, Sciences and Professions." Chagrin, later to be renamed in honor of its University "Willoughby," was at that time "a beautiful port town in the northeasternmost corner of Cuyahoga County—distance 20 miles northeast of Cleveland." The village had the advantages of a library, a lecture lyceum, a historical society, and a debating society where political, social, and scientific questions were discussed. About 1830, the era of railroads had begun to intrigue the public mind. One of the various railroad projects which promptly rose in Ohio was to have its terminus at the mouth of the Chagrin River. The villagers had visions of Chagrin becoming a great lake port. With these expectations came the yearning for a great university.

As a result, eleven citizens of the town, four physicians and seven laymen, were created a corporation under the name of Willoughby University of Lake Erie. Only the Medical Department, however, was organized. There were at least four reasons for this. In the first place there were several academies in the Western Reserve and graduation from any of these was considered in those days a great intellectual achievement and ample preparation for life unless perchance one were to enter one of the professions. Western Reserve College nearby at Hudson, Ohio, was already a flourishing institution eight years old—while the year before to the westward at no great distance, the Oberlin Collegiate Institute had opened its doors auspiciously so that there really was no great demand for an Arts College. In the second place, to the eastward there was no medical school nearer than the Fairfield Medical College in western New York—four hundred miles away. In Ohio, the only regular medical school was the fifteen year old Medical College of Ohio at Cincinnati, nearly three hundred miles distant. In addition, the irregular Reformed Botanic Medical School at Worthington was two years old. It is also to be remembered that there was no medical school in any of the states west of Ohio. Therefore it appeared to these enterprising citizens that there was room for a medical school in rapidly growing northern Ohio, for all these pioneer communities were more in need of physicians than for any other professional group. In the third place, there was the splendid figure and personality of Dr. Wetzel Willoughby, the founder of the Fairfield Medical School. He was interested in the town of



Drawn by Henry Howe in 1846.

Fig. 1. The Willoughby Medical School at Willoughby.

Chagrin financially and in the project of the school. To the school, he made liberal donations. It was only natural that his advice should direct the university at once to medical education. Finally, in those days medicine was the cheapest form of higher education to promote and operate.

While the four local physicians on the board of trustees naturally found themselves on the original faculty along with certain others including Storm Rosa of Painesville, who was later to become "The Stormy Petrel of Homeopathy," the faculty of the new school was largely recruited from that of the Fairfield School. It was possible in those days, due to the shortness of the annual sessions, for a professor to follow the example of the peripatetic professor of the Middle Ages, and hold as high as five chairs in five different schools, and not all of them the same chair either. While they were giving their lectures in Willoughby, these teachers "boarded around" with the good citizens of the town. Later there came several from the Berkshire Medical Institute. From these two schools came most of the early teachers and the ideals, more from Fairfield than from Berkshire. In general, it may be said that at the end, the Fairfield men went to Cleveland and founded the Cleveland Medical College while the Berkshire men came to Columbus. So this may have been the root of the trouble in the faculty at Willoughby as it developed through the years.

The faculty list from 1834 to 1847 contains the names of many of the outstanding educators in American Medicine.[1]

The faculty disagreed among themselves about many things. There was a growing local prejudice against practical anatomy and the way bodies were secured for dissection and demonstration. There were many administrative difficulties in the job of maintaining a salaried faculty in residence only during their own course. The professors and trustees discussed for some time the advisability of changing the location to a larger center of population as it became increasingly clear that Cleveland, and not Willoughby, was destined to be the metropolis of northern Ohio. Meantime, several of the faculty already lived and practiced in Cleveland. These naturally wanted to move the college to Cleveland, others did not.

In 1843, Delamater, Kirtland, Ackley, and Cassels resigned with the intention of organizing a school in Cleveland. This was done upon the gift of land and a sum of money. This was the beginning of the present day Western Reserve University School of Medicine.

Those who were left began to plan for the future of the school at Willoughby. Dr. John S. Butterfield, the man who was imported from the East upon the resignation of the Cleveland group for the chair

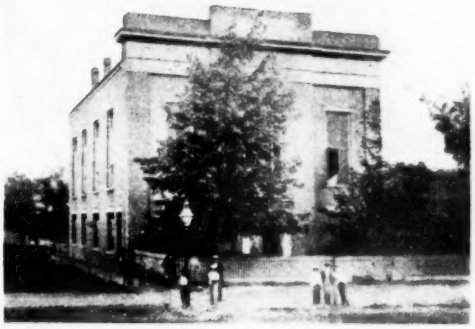


Fig. 2. The Wesley Chapel used for recitations and lectures by Willoughby Medical College of Columbus, Ohio.

of medicine, soon decided that the thing to do was to move the school to the rapidly growing capital of the state. Working with Dr. Richard L. Howard, Columbus' first surgeon, he was able to do this. By act of the Ohio legislature the charter was amended accordingly and The Willoughby Medical College of Columbus with a separate board of trustees came into being. It opened its doors for instruction on the seventh day of October, 1846. This session was held in a large frame building which had been moved from State Street to the northwest corner of Gay and High Street and remodeled into a small anatomical room and amphitheater with a seating capacity of 150. The next year additional room was secured by the rental of the basement of the Wesley Chapel a half block north. The faculty was composed of Henry Halsey Childs of Massachusetts; John Butterfield from Willoughby, now of Columbus; T. Rush Spencer of New York, also of the Willoughby faculty. The new teachers were Richard L. Howard of Columbus; Samuel M. Smith and Jesse P. Judkins of Cincinnati; Frederick Merrick of Delaware; and Norman Gay of Columbus.

It has been said that Lynn Starling, one of the founders of Columbus, was interested from the beginning in getting this school for his city and that he made a visit to Willoughby for the purpose of setting forth the advantages of Columbus. This we have not been able to verify. At any rate, the school and Starling's relatives, friends, and personal physician took a prominent part at once in its organization and direction. On December 18, 1847, Starling made a gift of thirty thousand dollars to the medical school on condition that *it would establish a hospital in connection with the school for the sick poor.* At a later date he added five thousand dollars more to his bequest.

[1]Horace A. Ackley, John Cook Bennett, T. W. Donovan, George Jones, William M. Smith, Francis Winthrop Walsh, Samuel Underhill, George W. Card, Hosmer Graham, Storm Rosa, Daniel Levi Madura Peixotto, John Lang Cassels, Amasa Trowbridge, Stephen West Williams, John Delamater, Orson Swift St. John, Jared Potter Kirtland, John S. Butterfield, Robert Hamilton Paddock, James Quackenboss, Isaac J. Allen, Henry Halsey Childs, George McCook, Abner Hartwell Brown, Thomas Rush Spencer—these were the men who served at Willoughby. "A number of them had long before established their claims to be regarded as men of high attainments—having been public teachers in our first medical schools of that day." The reader is referred to Frances Packard's *Medical History of the United States of America* for the details of the part that these men took in the other American medical schools of the time.

Fig. 3. The Starling Medical College and Hospital.

When the changes consequent upon Mr. Starling's donation had been completed, by a vote of the trustees and faculty, the name of the school was changed from the Willoughby Medical College of Columbus to the Starling Medical College. Mr. Starling had not asked for such change nor was it known that he expected it, but he accepted. So the Starling Medical College opened its first session with a new charter, incidentally to receiving the gift of $30,000 which up to that time was the largest gift that any citizen of Ohio had ever made to any institution. It was in the same building with the same equipment and the same Dean and faculty, with the addition of Dr. Francis Carter. There was, then, a strict continuity of work, purpose, and personnel. Upon these facts, the College of Medicine of the Ohio State University rests its claim that it is now in its one hundred and first year of teaching.

The frog-pond full of malaria on East State Street was purchased, largely because the citizens, almost to a freeholder, objected to having a medical school near their property. Plans were submitted by various architects. That of the present edifice of St. Francis Hospital, drawn by Mr. R. H. Shelden of New York, proved the most attractive. The estimated cost strangely enough was $35,000. This left nothing for endowment or equipment. The plans, however, were so attractive that the trustees decided to go ahead and build what proved to be the outstanding piece of architecture in the city and one of the finest of its type in the country.

The cost of the building turned out to be nearly twice the estimate. Thus the institution which started with a larger sum of money than any other medical school in the State was by the fourth year of its existence handicapped by a debt which constantly absorbed the greater part of its income until 1875. In 1853, the hospital part was completed and opened for patients. In 1854, private apartments were completed "nicely furnished and set apart for the special accommodation of females, who resort to them for the treatment of diseases peculiar to their sex." *This plan of having a hospital in connection with a medical school, owned and controlled by its trustees was years ahead of the times.* In 1855, the wards of the Ohio Penitentiary with its sick call of 30 to 60 patients per day was opened by legislative act to the medical students for their instruction.

In 1854, for reasons now obvious, the principle of a resident faculty was adopted in order that the teacher must devote a part of his time throughout the year to the development of the school. This new principle, of course, did away with the salaried lecturers from Pittsfield and Buffalo.

The history of the school now parallels that of other medical colleges in this country. Although attendance fell off, standards were raised and the instruction given was thoroughly adequate and as comprehensive as the development of medical science permitted at the time. The reputation of the local teachers grew and the school prospered. When the war between the states broke out, medical education in the United States was conducting itself upon a very high plane—higher than it was ever able to reach until after the Flexner report in 1909. With its well known and respected faculty, its own hospital, and its adequate equipment, the Starling Medical College occupied a most honorable position among American medical colleges.

The first outstanding contribution to medicine to come from the Starling Medical College was some twenty papers and finally in 1867, the *opus magnum* of Dr. T. G. Wormley, who at that time was professor of chemistry and toxicology. This work was an elaborate chemical and microscopical analysis of the nature and operation of many different poisons. It

Fig. 4. The Ohio Medical University and Protestant Hospital.

was the result of patient experimentation and cost the lives of some 2,000 cats and dogs.

In addition to Dr. Wormley, Dr. Starling Loving stood out in medicine and Dr. John Hamilton in surgery. These men were not only great teachers but great clinicians.

From 1857 to 1875 there were "few important changes and the classes gradually increased to respectable numbers." In 1875, the debt on the buildings was paid off and trouble started. Professors J. W. Hamilton, D. N. Kinsman, H. G. Pearce, and David Halderman, resigned and organized the Columbus Medical College. The effect of the simultaneous resignation of so many well known teachers, the founding of a rival school, and the addition of several new and untried men to the faculty, all served to diminish greatly the attendance. By 1879, however, the confidence of the profession and of the public had been in a large measure regained. From that time on the attendance was large and the college prospered.

THE COLUMBUS MEDICAL COLLEGE

For seven years, this college was conducted in the Session's Block on High Street. In January, 1882, it was transferred to a commodious college building on Long Street, which was especially constructed for the school.

On March 3, 1882, Dr. W. B. Hawk donated *to this college* four lots on the west side of the river and $10,000 for the erection of a hospital. About $10,000 was added to the original donation and an elegant hospital was erected in 1886. Thus began the Hawkes Hospital of Mt. Carmel.

The Columbus Medical College had a strong faculty and during the seventeen years of its existence it graduated about five hundred students.

In 1892, the Columbus Medical College suspended its operations as a separate teaching body and went back into the Starling Medical College.

THE OHIO MEDICAL UNIVERSITY

Certain of the teachers of the Columbus Medical College who did not return to the Starling Faculty joined with others in the organization of the Medical Department of the Ohio Medical University. This department together with those of Dentistry and Pharmacy began its first session on September 7, 1892, in a residence property at 775 North Park Street. At its inception the Ohio Medical University adopted the recitation plan of instruction and gave laboratory work and clinical medicine a prominent place in the course of instruction.

A lot was soon purchased and a university building, specially planned for its purposes, was erected on Park Street opposite Goodale Park.

In 1893, an agreement was entered into between the trustees of the Protestant Hospital, then occupying the present Radium Hospital, and the trustees of the Ohio Medical University by which the faculty of the school was to have exclusive charge of the clinical material of that hospital. The University donated the lot adjacent to the hospital on the south, and $5,000 to aid the erection of the hospital building which was completed in 1898.

The trustees purchased the lot adjoining the University on the north and erected thereon, in 1896, a large building for laboratory purposes.

In 1898, they erected another four-story structure facing the park. It has a modern gymnasium and bath rooms in the basement and a large assembly hall on the fourth floor. This building greatly enlarged the facilities and added to the architectural appearance of the University.

These institutions—Starling Medical College and the Ohio Medical University—at all times stood fully abreast with the best medical colleges in the West in elevating educational standards, meeting all the requirements of the Association of American Medical Colleges and the State Board of Medical Registration and Examination. They enforced the

Fig. 5. The College of Medicine, Ohio State University and its hospital.

three years' requirement for all students graduating from 1893–98, inclusive, and the four years' requirement of those graduating in 1899, the four-year graded course having been adopted by both colleges for all students graduating after January first of that year.

The amity of the colleges at the beginning of this century and their desire to enforce their announced requirements and to raise the standard of admission was attested by the agreement of both colleges to have a common examining committee, in no way connected with either college, to pass upon the credentials and preliminary education of all students.

THE STARLING-OHIO MEDICAL COLLEGE

In the spring of 1907, negotations were completed for the union of the Starling Medical College and the Ohio Medical University. Each school gave its own diplomas to its senior class and from then on operated as a single school.

During the days of the Starling-Ohio Medical College, too much credit cannot be paid to Dr. William J. Means, who, as dean, and professor of surgery, performed what to any one else would have been an impossible task. By persistence, he not only accomplished the merger with the Ohio State University, but he kept a first class medical school operating from student fees as its only source of income. In those days, Dean Means was a member of the inspection committee for the American Association of Medical Colleges. In this work he visited practically every medical college in the North American continent once every two years, and this in the company of such leaders as Dr. Waite of Western Reserve and Dr. Coldwell of the Council on Education of the American Medical Association. On return from each of these trips the good Dean would proceed to install all the ideas he had gotten which he could possibly use. Credit should also be given to the faculty who co-operated whole heartedly with this dean at the greatest personal sacrifice. Much of the inspiration for this sacrifice came from Professor Landacre and Dr. Ernest Scott.

It was obvious to those of us who were watching this Herculean effort of competing in performance without financial help with ever increasing endowments in other medical schools, that the limit must soon be reached. Dr. Thompson at the time of his election as president of Ohio State University had promised to postpone the establishment of a medical college until the time was ready. Dean Means was able to convince President Thompson that this was the time. The necessary legislation was secured to do this and to take over the Cleveland Pulte Homeopathic College, and so the University found itself with two colleges of medicine. With the completion of more than seven years (1907–14) of unremitting effort, Dr. Means was through. The same qualities which had made him a success as head of his own institution, unfitted him to find his way about in the maze of a large and now highly organized university. Like the prophet of old, he led his children into the promised land, but he himself could not enter.

Dr. Eugene F. McCampbell resigned his position as the state commissioner of health to succeed Dr. W. J. Means as dean of the College of Medicine of the Ohio State University. He set himself at once to the task of effecting a complete reorganization of the faculty along acceptable university lines. The number of the members of the faculty was cut nearly in two. Entrance requirements continued to be raised. Here it was again men like Drs. Landacre and Scott who gave the necessary support to these seemingly radical changes. Dr. Landacre accepted the chair of anatomy on condition that the department be put on a proper university basis, with recognition of the importance and scope of anatomy as a science, and not merely as a necessary part of the professional training of physicians. Both of these interests Professor Landacre guarded zealously, although it meant that he himself must assume the double load of teaching and the administration of both comparative vertebrate anatomy and human histology. The event has justified his idealism and the enormous labor which, during all these subsequent years, has been directed toward its realization by Dr. Landacre and loyal associates whom he had trained and inspired with his own ideals. As great as his contributions were, as administrative and teaching head of the department, and his careful work as secretary of the college faculty, it was, however, the high quality of his research that made him an inspiration to all. His

passing marked the fruition of a movement in the development of comparative neurology, which the world recognized as largely directed by his hand. His outstanding original contribution was an embryological analysis of the ganglia of the cranial nerves, with an exact and well controlled account of the origin and development of their components. Dr. Charles Judson Herrick of the University of Chicago, in his appreciation of the man, has recently written:

> His life was devoted to the Ohio State University; the intensity of this devotion and the immense labor and personal sacrifice by which he expressed it, have rarely been equaled. So quietly and modestly were his ideals of university standards of policy and practice advocated and enforced, that few people perhaps, even in his own community, realized their illustrious quality and the influence which he has actually exerted in shaping the course of medical education in American universities. He engaged in no propaganda. He wrote no papers. He made no speeches about medical education. He gave a practical demonstration of how it should be done and this was not done in a corner.

Dr. Ernest Scott, who for thirty years occupied the chair of pathology in this college, contributed more than any one man to the success of the school in those days. He was sympathetic and stimulating with the individual student. To both the student and his colleagues, his entire efforts and extreme honesty were an inspiration. These qualities he gave to the school at great personal sacrifices, and thereby contributed a major part to blending the medical college into the life of the university as a whole.

Dr. McCampbell came to the deanship excellently prepared for the job before him. No sooner had he reorganized the faculty, than he began to lay the plans for a group of medical buildings on the campus. Characteristic of the man, he accomplished his task and Hamilton Hall and the Starling Loving Hospital at Neil Avenue stand as a monument to his labors. His success marked the passing of the College of Homeopathic Medicine.

After every period of material expansion, there must follow a period of internal growth, and so that servant of the American Medical Association, for years a member of its board of trustees, Dr. J. H. J. Upham, was chosen to be Dr. McCampbell's successor as dean. Objectives were consolidated under his leadership. The Department of Experimental Medicine and Surgery was established and manned by distinguished scientists.

Ohio State is proud of the hundred years of progress in its College of Medicine. Ohio State has a noble heritage which she views with pride and in humility as she begins the new Century.

Acknowledgment is made for the liberal use of material from the *History of the College of Medicine of the Ohio State University* recently published by a committee of which this author was chairman—and from which the accompanying cuts were borrowed.

APPENDIX

Out of this century of progress there have come certain outstanding contributions to American medicine. They are—

1. Dr. T. G. Wormley's work on poison (1869).
2. Dr. J. W. Wright—who first invented the intracapsular enucleation of the lens for cataract by expression (1884).
3. Dr. T. D. Gilliam—who brought forward the basic method for uterus suspension by means of the round ligaments (1900).
4. Dr. James Fairchild Baldwin—who presented in 1904 what is now known as the Baldwin operation. A method for the formation of an artificial vagina in the case of the absence of that organ (1909).
5. Dr. Francis Leroy Landacre—a lifetime of research devoted to an embryological analysis of the ganglia of the cranial nerves (1900–1934).
6. Dr. Roy Graham Hoskins—series of papers on the adrenal gland which prove that its secretion is not necessary for the maintenance of a normal blood pressure (1911).

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

THE publication of a second edition of Codman's *The Shoulder*[1] gives an opportunity to draw attention to something unique in medical books and to recommend a volume that should be in the library of every surgeon and practitioner who deals with injuries about the shoulder. Besides being a valuable contribution to a poorly understood subject, it is pervaded with the sincere and purposeful personality of the pioneer in this field. It is more than a dry textbook of scientific observations. It attacks one of the fundamental problems of present-day surgery—the failure of surgeons to follow through cases of such injuries to determine the final end-results and the value of the various methods of treatment. It would naturally be expected that Dr. Codman would emphasize this problem, for all his life he has fought for the principle of "evaluating the end-results of surgery."

The preface and epilogue of the book, in addition to being most readable, are enlightening and stimulating as the philosophy of the inquiring mind. As the American College of Surgeons adopted and fostered his earlier advocacy of analyzing "End-Results" he has addressed his remarks to its fellows.

Dr. Codman's early contribution upon subacromial bursitis still stands as a classic in surgical literature, and his present study of rupture of the supraspinatus tendon has aroused our interest, clarified a new entity, and if he succeeds, as undoubtedly he will, in making the general profession realize the importance of these injuries, he will have restored many patients threatened with life-long disability to comfort and efficiency—to say nothing of the hundreds of thousands of dollars he will save for casualty companies.

To make the profession "shoulder conscious," Dr. Codman advocates that all hospitals make, for a time, a combined study of the shoulder. Internes especially should have their attention focused on the lesion, and all cases of shoulder injury not recovering promptly should be presented at staff conferences. He is right in believing that this will result in time in prompt recognition of obscure lesions and the institution of early proper treatment by which the present inadequate and costly care may be avoided. Dr. Codman pleads for the same treatment to be applied in any contribution dealing with new principles or innovations so that an early evaluation may be secured. Hospital staffs should be proving grounds. Thus the efficiency of hospitals would be elevated and proven procedures be made promptly available to the profession.

The various chapters cover the anatomy, normal motions and pathology in general and consider specifically arthritis, bursitis, rupture of tendons, deposits in the joint, tendinitis, brachial plexus paralysis, neuroses, malingering, tumors, and similar subjects. Dr. Codman's technique of treatment is exhaustively treated with appropriate case reports and illustrations—a contribution of 500 pages all worth reading.

[1] THE SHOULDER. RUPTURE OF THE SUPRASPINATUS TENDON AND OTHER LESIONS. By E. A. Codman, M.D. Privately printed. E. A. Codman, 227 Beacon St., Boston. Price $10.00.

THE fifth edition of *Diseases of Women*[1] shows considerable revision and improvement. Like previous editions, it is a collective effort of ten of the leading gynecologists of England. It is simply and tersely written and is unusually well illustrated. It should be a valuable work for students in gynecology, including as it does, a complete section on the principles of technique of gynecological surgery.

The chapters on ectopic pregnancy are well written and there is an excellent and important chapter on chronic ill health from the psychological standpoint; neurasthenia in relation to pelvic disorders, a subject that American textbooks might do well to include.

The discussion of ovarian functions and the entire discussion of the endocrines have been brought up to date. These sections are exceptionally well written, as is the one dealing with the disorders of menstruation.

The American gynecologist will disagree with the liberal use recommended for the uterine sound, the methods for the examinations of the discharges, and the fact that anesthesia is still recommended for the Rubin insufflation test. In this edition the use of the electric cautery in cervical disease is included for the first time. However, the pleasing and informal style in which the entire book is written, together with the fact that it presents an accurate picture of British gynecology of today, should make this volume a desirable addition to the gynecologist's library. RALPH A. REIS.

RECENTLY there have been published a number of small monographs which have dealt with the description of a series of intracranial tumors of

[1] DISEASES OF WOMEN. By Ten Teachers under the direction of Comyns Berkeley, M.A., M.D., M.C. (Cantab.), F.R.C.P. (Lond.), F.R.C.S. (Eng.), M.M.S.A. (Hon.), F.C.O.G. Edited by Comyns Berkeley, J. S. Fairbairn, and Clifford White. 5th ed. Baltimore, Maryland: William Wood & Co., 1934.

rather rare occurrence. Dandy's volume[1] is devoted to the benign and encapsulated tumors which occur in the lateral ventricle of the brain. The literature is replete with reports of tumors arising from the choroid plexus and within the ventricles which are masked under many various names.

Probably one of the most important steps which has been made in the progress of the knowledge concerning intracranial tumors has been a careful study of the tumors removed with regard to their histological characteristics and their exact origin. Accompanying these studies in importance has been the correlation with the clinical course of the patient. In such a manner the rapidity of development of a particular group of tumors, their behavior after surgical treatment, and their reaction to X-ray or radium therapy may be learned.

For example, in 1925, a report from Cushing's clinic called attention to the difficulty of sorting from the literature those tumors which project into the ventricles but originated elsewhere. This report was concerned only with the characteristics of the tumors originating from the choroid plexus. Because of their typical papillomatous, cauliflower-like appearance, both grossly and microscopically, they were called papillomas of the choroid plexus. While Dandy does not speak of papillomas of the plexus it may be that he refers to the tumors under the name of adenomata, a term neither so descriptive nor as accurate. This use of another term to describe the same tumor only adds to the confusion which already exists in the literature and does not help clarify the situation. Again, while Dandy includes two of the tumors reported from Cushing's clinic in his list of those "probable benign growths" he omits others which were exactly similar histologically and which had an analogous clinical history. One does not get a very clear and easily understandable view of the pathological characteristics of the author's tumors.

The rôle played by ventriculography in the diagnosis and treatment of these intraventricular tumors, many of which are devoid of localizing symptoms, is an important one. One should not be misled as to the ease of their removal by the excellent illustrations shown in the text.

It is unfortunate that the last twenty pages of the reviewer's copy of this monograph which contain the pathological, clinical, and surgical summaries and conclusions are unreadable because of pages which are upside down and transposed completely in their order. One cannot help but believe that a more concise and helpful story of these tumors might have been written in a shorter article planned with more effectiveness. L. D.

A REVIEW of the activities of the Premature Infant Station at the Sarah Morris Children's Hospital of the Michael Reese Hospital, during the station's first 12 years, together with an intimate study of the physical and mental development of two hundred and fifty older graduates from this station, is contained in *The Physical and Mental Growth of Prematurely Born Children*.[1] It is the first comprehensive and scientifically documented study of the clinical observations of a large number of prematurely born infants. The book is published as one of the Behavior Research Fund Monographs, sponsored by the Illinois Institute for Juvenile Research.

This monograph is divided into three main portions. In Part 1, 57 pages, Dr. Julius Hess discusses the history and development of this Premature Infant Station, the clinical material, the etiological factors influencing prematurity, the morbidity and mortality during first admission and after graduation, and the clinic for graduates. In Part 2, 143 pages, Dr. George Mohr and Phyllis Bartelme describe the results of careful research work upon the significant problem of the degree of differences in physical and mental status of children of premature and full term birth. These studies continue the story of prematurity into youth and present graphic analyses of intelligence, emotion, habit, and social adaptation among premature infants as compared with their siblings, and with the general average groups of Binet and Gesell norms. The authors are very cautious in drawing conclusions which makes the scientific work more impressive regarding the nature and extent of the effect of congenital injuries and other conditions upon the later physical and mental development of the child.

In addition to these general studies, there are in Part 3, ten special papers on individual points of the problems, pertaining to the most frequently observed pathological conditions among the prematurely born infants such as intracranial hemorrhage, syphilis, anemias, cerebrospinal fluid, oxygen therapy, hernias, etc., each subject written by physicians who have made special studies of these problems at the Permature Station.

There are 161 tables, both statistical and graphical, and 90 illustrations showing among other things the special equipment developed by Dr. Hess and his associates at the Premature Infant Station.

It is an excellent study, probably the only one of its kind, and answers the question, "What is the ultimate outlook for the prematurely born infant?"

JOSEPH K. CALVIN.

IN a very extensive and elaborate publication[2] Belou covers the arteries of the human body below the diaphragm. Volume 3, part 2, is a part of a stereoscopic atlas, though a few of the illustrations are simple photographs. Most of the reproductions are made by a photographic process on sensitive paper, only a few being half-tone reproductions. The photographs and roentgenograms

[1] BENIGN, ENCAPSULATED TUMORS IN THE LATERAL VENTRICLES OF THE BRAIN; DIAGNOSIS AND TREATMENT. By Walter E. Dandy, M.D. Baltimore: The Williams & Wilkins Co., 1934.

[1] THE PHYSICAL AND MENTAL GROWTH OF PREMATURELY BORN CHILDREN. By Julius H. Hess, M.D., George J. Mohr, M.D., and Phyllis F. Bartelme, Ph.D. Chicago: The University of Chicago Press, 1934.

[2] REVISION ANATOMICA DEL SISTEMA ARTERIAL. By Pedro Belou. Part 2. Buenos Aires, 1934.

presented in this atlas have been selected from the large collection in the museum of the Department of Anatomy of the Faculty of Buenos Aires, totaling 123 color photographs, 2500 stereo-arteriograms. Words can hardly portray the beauty and the extreme delicacy of detail of the photographs of the injected preparations. Many photographs of anatomical preparations are presented to clarify the discussion on the arteriograms. The stereoscopic method of arteriography has made it possible for the anatomist to analyze in finest detail the manner in which the arteries enter the muscles, their origins and the number of branches to each muscle, the caliber of the major trunks, their direction and length, the points at which they penetrate the body of the individual muscles, the final distribution of the muscular arteries, whether to muscles and nerves, to muscles and periosteum, or to muscles and skin. It has also made it possible to confirm the existence of the anastomotic reticular network of Spalteholz as well as the larger intramuscular anastomoses.

We heartily congratulate Belou on his beautiful work and the Medical Faculty which has sponsored this valuable anatomical contribution.

JAMES T. CASE.

IT is the wish of Goldthwait[1] and his coworkers to instill greater interest on the part of the physician in the care of the *chronic* patient, and desire a better understanding of the important physiological changes secondary to altered body mechanics. It seems to them that solution of the problem is closely related to the treatment of altered body mechanics.

In a general consideration of the mechanics of the body, the co-relation of the structures, bones, muscles, and ligaments is discussed. The mechanics of the spine receive special attention. Much importance is ascribed to the position of the diaphragm, which is said to affect circulation and abdominal and pelvic organs as well as respiratory system.

Body types are divided into three classes—the slender, the so called normal, and the stocky. The slender type, according to the authors, may have a tendency to eye strain and high metabolism; they have greater potentiality for varicosities; their blood pressure is often low; even psychological inclinations are attributed to this body type, such as a poorly developed sense of humor and a tendency to be dogmatic and fanatic. The heavy type have associated high blood pressure, ruddy countenance, tendency to become fat, low metabolism, good temper.

A case report of a man with backache is used to demonstrate the altered anatomical changes and their effects on the physiology of the body as a whole. The problem of arthritis is taken up from the point of view of strains caused by habitual bad posture. Importance is attached to the position of the abdominal organs with regard to their function; the drag of the congested organs on the nerve supply as well as the pressure upon the sympathetic ganglia and plexuses is believed to cause some irregularity in function.

In treatment the authors utilize rest in bed and certain kinds of exercises and various types of braces. They emphasize the need of active co-operation of the patient and education of the individual as to his condition. Properly planned exercises and, for severe cases, various methods of obtaining relaxation in the recumbent position are described. Proper posture and the value of muscle control are stressed.

Case reports follow which demonstrate the effect of the improvement in body mechanics in conditions varying from Still's disease to multiple sclerosis.

EMIL D. W. HAUSER.

[1] BODY MECHANICS IN THE STUDY AND TREATMENT OF DISEASE. By Joel E. Goldthwait, M.D., LL.D., Lloyd T. Brown, M.D., Loring T. Swaim, M.D., and John G. Kuhns, M.D. Philadelphia, London, and Montreal: J. B. Lippincott Co., 1934.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

DIE BEDEUTUNG DER VITAMINE FUER DAS WEIB. By Prof. Dr. Hans Guggisberg. Berlin and Vienna: Urban & Schwarzenberg, 1935.

THE TREATMENT OF RHEUMATISM IN GENERAL PRACTICE. By W. S. C. Copeman, M.A., M.B., B.Ch.(Cantab.), M.R.C.P.(London). With a foreword by Sir William Hale-White, K.B.E., M.D., F.R.C.P., Hon. LL.D. 2d ed. Baltimore: William Wood & Co., 1935.

CHRONIC NASAL SINUSITIS AND ITS RELATION TO MENTAL DISORDER, etc. By F. A. Pickworth, B.Sc., M.B., B.S., A.I.C.(Exam.) London: H. K. Lewis & Co., Ltd., 1935.

CLINICAL MANAGEMENT OF SYPHILIS. By Alvin Russell Harnes, M.D. New York: The Macmillan Co., 1935.

MANUAL OF MEDICINE. By Sir Stanley Woodwark, C.M.G., C.B.E., M.D., F.R.C.P. 4th ed. London: Oxford University Press, 1935.

THE METHOD OF ACTION OF RADIUM AND X-RAYS ON LIVING TISSUES. By Hector A. Colwell, M.B., Ph.D., M.R.C.P., D.P.H. London: Oxford University Press, 1935.

THE WOMAN ASKS THE DOCTOR. By Emil Novak, M.D., F.A.C.S. Baltimore: The Williams & Wilkins Co., 1935.

MANUAL OF DIABETES. By J. J. Conybeare, M.C., M.D., F.R.C.P. London: Oxford University Press, 1935.

TEXT-BOOK OF UROLOGY. By Daniel N. Eisendrath, M.D., and Harry C. Rolnick, M.D. 3d rev. ed. Philadelphia and London: J. B. Lippincott Co., 1935.

ORTHOPEDICS FOR THE TEACHERS OF CRIPPLED CHILDREN. By Samuel W. Boorstein, M.D., F.A.C.S. New York: Aidem Publishing Co., 1935.

TRANSACTIONS OF THE AMERICAN GYNECOLOGICAL SOCIETY. Volume 59 for the Year 1934. Edited by Otto H. Schwarz, M.D. St. Louis: C. V. Mosby Co., 1935

CLINICAL CONGRESS OF AMERICAN COLLEGE OF SURGEONS

ROBERT B. GREENOUGH, Boston, *President* DONALD C. BALFOUR, Rochester, *President-Elect*

HOWARD C. NAFFZIGER, *Chairman;* THOMAS F. MULLEN, *Secretary, Committee on Arrangements*

PRELIMINARY CLINICAL PROGRAM FOR THE 1935 CLINICAL CONGRESS

A PRELIMINARY program of clinics and demonstrations arranged for the twenty-fifth annual Clinical Congress of the American College of Surgeons to be held in San Francisco and Oakland, October 28 to November 1, as prepared by the local Committee on Arrangements, appears in the following pages. It will be noted that operative clinics and demonstrations in the hospitals are scheduled for the afternoon of Monday, October 28, beginning at two o'clock and for the mornings and afternoons of each of the four following days. The clinical program, published in tentative form at this time, is to be revised and amplified during the next three months as the work of the program committee progresses. Assured of the hearty co-operation of the clinicians at the two medical schools and twenty-seven hospitals that will participate in the clinical program, the Committee plans to provide a program of surgical clinics in the hospitals and schools of that great medical center on the Pacific coast that will present a complete showing of their clinical activities in all departments of surgery.

The Committee expects to develop many special features in the clinical program including: (1) Cancer clinics demonstrating the treatment of cancer by surgery, radium and X-ray; (2) fracture clinics demonstrating modern methods of treatment; (3) clinics in traumatic surgery demonstrating the newer methods of rehabilitation of injured patients by surgery and physiotherapy.

The sub-committee in charge of the section on surgery of the eye, ear, nose, and throat, in addition to arranging for a series of ophthalmological and otolaryngological clinics and demonstrations in the hospitals and medical schools, is preparing programs for scientific sessions at headquarters on Tuesday, Wednesday, Thursday and Friday mornings at which distinguished specialists in these branches of surgery will present and discuss papers on subjects of clinical interest.

EVENING MEETINGS

Programs for the series of five evening sessions is being prepared by the Executive Committee of the Board of Regents. The presidential meeting on Monday evening will be held in the Municipal Opera House at which the retiring president, Dr. Robert B. Greenough, of Boston, will deliver the annual address. Officers elected at the 1934 Clinical Congress are to be inaugurated—Dr. Donald C. Balfour, Rochester, president; Dr. Arthur W. Allen, Boston, and Dr. John A. Gunn, Winnipeg, vice-presidents. At that session Dr. George Crile, of Cleveland, will deliver the American College of Surgeons oration on surgery. On Tuesday, Wednesday and Thursday evenings the sessions will be held in the Auditorium of the Veterans' Building at which eminent surgeons of the United States and Canada, together with visiting surgeons from foreign countries, will present papers dealing with surgical subjects of timely importance. On Friday evening the annual convocation will be held in the Municipal Opera House, at which the 1935 class of initiates will be received into Fellowship in the College. Dr. Robert Gordon Sproul, president of the University of California, will deliver the Fellowship address.

SPECIAL FEATURES

Special features of the program for this year's Congress include: (1) A conference on fractures on Tuesday afternoon, the program being arranged in co-operation with the College Committee on the Treatment of Fractures. (2) A cancer symposium on Thursday afternoon under the auspices of the College Committee on the Treatment of Malignant Diseases will present additional statistics on the cure of cancer as reported by clinicians from various parts of the United States and Canada, with a number of papers descriptive of approved methods for the treatment of cancer as developed and employed in the lead-

ing medical centers. (3) A conference on Friday afternoon dealing with many of the problems being studied by the Board on Industrial Medicine and Traumatic Surgery. All of these sessions will be held in the Gold Ballroom of the Fairmont Hotel.

Surgical motion picture films, both sound and silent will be exhibited daily at headquarters at the Fairmont Hotel. Such surgical motion picture film exhibitions have met with popular acceptance in recent years, and an extensive and varied exhibit, including many new films, is planned for this year's Congress.

THE CLINICAL CONGRESS AND A VACATION TRIP TO THE PACIFIC COAST

In planning to attend the Clinical Congress in San Francisco this fall, the natural suggestion is to make this a vacation trip, the advantages of which will appeal to the Fellows of the College and their guests. The railways offer very low round-trip rates, with liberal stopover privileges, from all parts of the United States and Canada, with the added privilege of traveling to the coast by one route and returning via another, affording unusual opportunities for visiting many points of interest enroute.

Few cities have so impressive a setting as San Francisco. The rugged hills upon which it is built, the Golden Gate, Mt. Tamalpais, the misty bay to the east, Oakland and Berkeley and the hills beyond, all contribute to its grandeur. It is a pleasing picture and the citizens of San Francisco have not been unmindful of it. Their parks and residence districts have a dignity and beauty in keeping with the scene about them.

The glamour of the city is inescapable, but no amount of description can picture accurately this unique city. One must see for himself how the many charming aspects of San Francisco and its environs blend into one delightful and unforgettable picture.

While on the coast one will naturally wish to see as much of the great west as possible and will find it surprisingly easy to visit the "high spots" in a relatively short time and at a reasonable cost. A round trip ticket at low summer rates permits one to visit scores of interesting points on the Pacific coast by having the ticket read via one route on the western trip and another route for the return trip.

Along the Pacific coast one will find much to claim his attention. First, there is the California-Pacific International Exposition at San Diego—a World's Fair of magnitude, with many important medical and other scientific exhibits—erected in Balboa Park, a tropical fairyland. The buildings, which are permanent structures, have their dignity and beauty enhanced by the gorgeous setting.

Los Angeles with its mountain background, its broad boulevards, its nearby beaches, its hospitality—and Hollywood—afford opportunities for entertainment and recreation. A one-day trip to enchanting Catalina Island with its balmy south sea island atmosphere, naturally suggests itself.

A ride through the San Joaquin Valley to the Yosemite, sublime at all times, but with autumn coloring will be unforgettable. Del Monte and Pebble Beach on the famous seventeen mile drive are but a short distance from San Francisco. Other nearby points of interest are Paso Robles, with its almond groves, lovely Santa Barbara with its famous Old Mission, and a score of cities whose names are associated with the romantic Spanish period—a fairyland of natural and cultivated beauty.

To the north there are many cities to claim your attention: Vancouver, in British Columbia, built up against mighty mountains with a primeval forest almost at its environs. Seattle, the great shipping center of the northwest, with Puget Sound to the west and beyond it the white-capped Olympics. In the distance the Cascade Mountains and looming to the southeast, Mt. Rainier, held in special veneration by the Indians as "the mountain that was God"—no peak in the United States is so majestic. Portland, famous for its natural beauty—a literal bower of roses. The blue miracle of Crater Lake, Mt. Shasta and Mt. Lasson, the only active volcano in the United States.

No matter what route one takes he will view a truly great and inspiring American scene—the thriving farm lands of the midwest, the noble stretches of prairie, the sublime mountain ranges of the Rockies, the grandeur of the desert, the towering forests of the far west, and then the blue Pacific.

This year one will travel in comfort and luxury undreamed of a short time ago. Whatever route one travels he will find his train air-conditioned. This single factor adds so much to the comfort and pleasure of a transcontinental journey that it definitely and certainly marks the beginning of a new era in transportation history.

HOSPITAL CONFERENCE

The annual hospital conference will open the Congress with a session in the Gold Ballroom of the Fairmont Hotel at 10 o'clock on Monday morning. An interesting program of papers, round

table conferences and practical demonstrations dealing with problems related to hospital efficiency is being prepared for sessions to be held on Monday, Tuesday, Wednesday and Thursday in the Gold Ballroom of the Fairmont Hotel, and at several of the hospitals. A greatly increased interest on the part of surgeons in both the administrative and scientific phases of hospital work has been evidenced in recent years and the program for this year's conference will be unique in providing for discussions of subjects of interest to the three major hospital groups—medical, surgical and administrative. It is planned to make this year's program of wide interest and practical character through a careful selection of subjects to be presented and discussed by surgeons and hospital executives, particular emphasis being directed toward professional standards and the vital problems related to medical economics.

HEADQUARTERS—TECHNICAL EXHIBITION

Headquarters for the Congress will be established at the Fairmont and Mark Hopkins hotels. At the former the Terrace Ballroom and Lounge, the Gold Ballroom and other large rooms on the main floor and on the terrace have been reserved for scientific sessions and conferences, registration and clinic ticket bureaus, bulletin boards, exhibits, executive offices, etc. The Peacock Court and Room of the Dons at the Mark Hopkins will be utilized for various scientific sessions.

The Technical Exhibition, including the registration and clinic ticket bureaus, will be located in the ballroom and lounge on the terrace floor of the Fairmont Hotel. In these rooms will also be found the bulletin boards on which the daily clinical program will be posted each afternoon. The leading manufacturers of surgical instruments, X-ray apparatus, operating room lights, hospital apparatus and supplies, ligatures, dressings, pharmaceuticals and publishers of medical books will be represented in this exhibition.

ADVANCE REGISTRATION

The hospitals and medical schools of San Francisco and Oakland afford accommodations for a large number of visiting surgeons, but to insure against overcrowding, attendance at the Congress will be limited to a number that can be comfortably accommodated at the clinics—the limit of attendance being based upon the result of a survey of the amphitheaters, operating rooms, and laboratories of the hospitals and medical schools to determine their capacity for visitors. It is expected, therefore, that those surgeons who wish to attend the Congress will register in advance.

Admittance to all clinics and demonstrations will be controlled by means of special clinic tickets, which plan provides an efficient means for the distribution of the visiting surgeons among the several clinics and insures against overcrowding, as the number of tickets issued for any clinic will be limited to the capacity of the room in which that clinic will be given.

A registration fee of $5.00 is required of each surgeon attending the annual Clinical Congress, such fees providing the funds with which to meet the expenses of the meeting. To each surgeon registering in advance a formal receipt for the registration fee is issued, which receipt is to be exchanged for a general admission card upon his registration at headquarters. This card, which is non-transferable, must be presented in order to secure clinic tickets and admission to the evening meetings.

SAN FRANCISCO HOTELS AND THEIR RATES

In addition to the two headquarters hotels—the Fairmont and Mark Hopkins—there are a number of first-class hotels within short walking distance of headquarters providing ample hotel facilities at reasonable rates. The following hotels are recommended by the Committee:

	Minimum Rate with Bath	
	Single	Double
Bellevue, Geary and Taylor	$3.00	$4.00
Californian, Taylor and O'Farrell	3.00	4.50
Clift, Geary and Taylor	3.50	5.00
El Cortez, Geary near Taylor	3.00	4.50
Fairmont, Mason and California	3.50	5.00
Gaylord, Jones near Geary	3.00	4.00
Mark Hopkins, Mason and California	3.50	5.00
Palace, Market and New Montgomery	3.50	5.00
Plaza, Post and Stockton	3.00	4.00
Sir Francis Drake, Powell and Sutter	3.50	5.00
Stewart, 353 Geary	2.50	4.00
St. Francis, Union Square	3.50	5.00

COMMITTEE ON ARRANGEMENTS

Executive Committee

Howard C. Naffziger, Chairman; Thomas F. Mullen, Secretary

Leroy C. Abbott
Harold Brunn
Edmund Butler
Whitfield Crane
Charles A. Dukes
Leo Eloesser
Philip K. Gilman
Oliver D. Hamlin
Frank Hinman
Emile F. Holman
Alson R. Kilgore
Frank W. Lynch
Joseph L. McCool
Isaac W. Thorne

SUB-COMMITTEES—SAN FRANCISCO

Clinical Program Committee (General Surgery)—Alson R. Kilgore, Chairman; Edmund Butler, Thomas F. Mullen.

Clinical Program Committee (Eye, Ear, Nose and Throat Surgery)—Joseph L. McCool, Chairman; H. B. Graham, Warren D. Horner.

Transportation Committee—Emile F. Holman, Chairman; G. D. Delprat, Millard R. Ottinger.

Public Meeting Committee—Jacob C. Geiger, Chairman; Harold M. Behneman, Edgar L. Gilcreest, Jacques P. Gray, Leon Wilbor.

Golf Committee—Leroy Brooks, Chairman; Harry Alderson, James Morgan, Frank Sheehy.

HOSPITAL REPRESENTATIVES

SAN FRANCISCO—GENERAL SURGERY

Franklin Hospital—Ernst Gehrels, Leroy Brooks.

French Hospital—Asa Collins, Edmund Morrissey.

Hospital for Children—Leroy Abbott, Alma Pennington.

Letterman General Hospital—R. T. Metcalfe.

Mary's Help Hospital—Isaac Thorne, Raymond Millzner, Everett Carlson, Dudley Smith.

Mount Zion Hospital—Harold Brunn, Franklin Harris, Albert L. Brown.

St. Francis Hospital—James O'Connor, Calvin A. Walker.

St. Joseph's Hospital—Alson R. Kilgore, J. Minton Meherin.

St. Luke's Hospital—G. D. Delprat, Otto Pflueger.

St. Mary's Hospital—Thomas E. Bailly, Philip Arnot, Daniel Sooy.

San Francisco Hospital—Stanford University Service: Leo Eloesser, H. Matthewson, L. Rogers. University of California Service: Harold Brunn, C. Latimer Callander, George K. Rhodes.

Shriners' Hospital for Crippled Children—Sylvan Haas.

Southern Pacific General Hospital—William Washburn, Frank R. Girard.

Stanford University Hospitals—Emile Holman, Philip K. Gilman, Frederick Reichert.

Stanford University School of Medicine—Loren Chandler, Emmet Rixford.

United States Marine Hospital—Mark J. White Richey L. Waugh.

University of California Hospitals—Howard C. Naffziger, H. Glenn Bell.

University of California Medical School—Langley Porter, Wallace Terry.

Veterans Administration Hospital—P. E. Johnson, Berthel H. Henning, John A. Kennedy.

SAN FRANCISCO—SURGERY OF THE EYE, EAR, NOSE AND THROAT

French Hospital—Edward C. Fabre-Rajotte, Victor d'Ercole.

Hospital for Children—George Hosford.

Letterman General Hospital—A. E. Schlanser, H. C. Maxwell.

Mary's Help Hospital—Frank Hand, J. W. Crawford.

Mount Zion Hospital—Frank Rodin, Herbert Cohn.

St. Francis Hospital—Constantine Bricca, Aubrey Rawlins.

St. Joseph's Hospital—Roy Parkinson.

St. Luke's Hospital—Ambrose E. Edgerton, Charles Bates.

St. Mary's Hospital—Francis Conlan, Stanley Burns.

Southern Pacific General Hospital—Wilbur Swett.

Stanford University Hospitals—Edward Sewell, Hans Barkan, Harrington Graham, Louis Morrison.

United States Marine Hospital—Rae Ashley.

University of California Hospitals—Wallace Smith, Fred C. Cordes, Robert C. Martin, C. Allen Dickey.

Veterans Administration Hospital—J. J. Caviness, Otto Barkan.

OAKLAND EXECUTIVE COMMITTEE

Oliver D. Hamlin, Chairman
Charles A. Dukes, Vice Chairman
Whitfield Crane, Secretary

Clinical Program Committee—Lemuel P. Adams, Warren B. Allen, Harry H. Appledorn, Frank S. Baxter, Julian J. Benton, Whitfield Crane, Charles A. Dukes, Sumner Everingham, Channing Hall, Oliver D. Hamlin, Henry W. Harding, Harold H. Hitchcock, T. O. Lake, Theodore C. Lawson, Ergo Majors, W. Earl Mitchell, George McClure, Albert Meads, Raymond J. Nutting, Clair Rasor, Dextor N. Richards, Milton H. Shutes, H. R. Smithies, Clifford Sweet, Frank Walsh, Don D. Weaver.

PRELIMINARY CLINICAL PROGRAM

GENERAL SURGERY, GYNECOLOGY, OBSTETRICS, ORTHOPEDICS, UROLOGY, SURGICAL PATHOLOGY, ETC.

OPERATIVE CLINICS IN SAN FRANCISCO HOSPITALS—DAILY

SAN FRANCISCO HOSPITAL

University of California Service

HAROLD BRUNN, GEORGE K. RHODES, A. R. KILGORE, C. L. CALLANDER, S. H. MENTZER, A. L. BROWN, H. W. STEPHENS, F. S. FOOTE, M. W. DEBENHAM, H. M. BLACKFIELD and L. GOLDMAN. General surgery.

F. HINMAN, C. JOHNSON, S. OLSEN, L. PLAYER, J. J. SULLIVAN, W. A. CARROLL and T. O. POWELL. Urological operations.

W. G. MOORE, A. M. VOLLMER and M. SCHULZE. Gynecological operations.

H. W. FLEMING, H. A. BROWN and L. B. LAWRENCE. Neurosurgical operations.

LEROY ABBOTT, F. G. LINDE, F. C. BOST, W. J. COX and K. O. HALDEMAN. Orthopedic operations.

Stanford University Service

LEO ELOESSER. Lobectomy for lung tumor; flap operation for tuberculous empyema; disarticulation at knee joint.

W. L. ROGERS. Apicolysis (paraffin fill).

J. M. MEHERIN. Gastric resection (Billroth I).

EDMUND BUTLER. Pyloroplasty for peptic ulcer; atresia of colon, congenital.

J. CLINE. Exploration of biliary duct.

C. MATHEWSON. Open reduction of spiral fracture of the tibia; sequestretomy for tuberculosis of the pelvis.

D. KING. Nonunion of carpal scaphoid.

M. R. OTTINGER. Resection for carcinoma of the colon.

E. TOWNE. Laminectomy for decompression of cauda equina.

E. MORRISSEY. Removal of cord tumor.

L. REYNOLDS. Cystectomy for carcinoma of the bladder.

G. HARTMAN. Suprapubic prostatectomy.

L. MICHAELSON. Plastic on kidney pelvis.

R. CRAIG. Nephrectomy.

K. SCHAUPP. Removal of fibromyoma of the uterus.

A. PETTIT. Vesicovaginal fistula.

H. VON GELDERN. Perineal repair operation.

C. COOLEY. Operation for pelvic inflammatory disease.

R. DUNN. Hyam's conization of the cervix.

D. DALLAS. Vaginal hysterectomy.

UNIVERSITY OF CALIFORNIA HOSPITAL

HOWARD C. NAFFZIGER, D. JONES, JR., H. BROWN and R. AIRD. Neurosurgical operations.

HAROLD BRUNN and H. STEPHENS. Thoracic surgery.

R. ABBOTT, F. BOST, K. HALDEMAN and W. KEYS. Orthopedic surgery.

A. MAXWELL, M. SCHULTZE, D. MORTON and C. HAYDEN. Gynecological and obstetrical operations.

FRANK HINMAN, C. JOHNSON, S. OLSEN and B. WAYMAN. Urological operations.

W. S. TERRY. General surgical operations; thyroidectomy.

H. SEARLS and H. GLENN BELL. Carcinoma of colon; cholecystectomy; popliteal aneurism.

C. ROSSEN. Appendectomy; hernioplasty.

M. S. WOOLF. Carcinoma of rectum and lower bowel.

F. FOOTE. Partial obstruction, new operations.

E. O. BARTLETT. Carcinoma of breast.

STANFORD UNIVERSITY HOSPITAL

EMMET RIXFORD, EDMUND BUTLER, R. GILMAN, L. CHANDLER, EMILE HOLMAN and S. BUNNELL. General abdominal surgery; gastro-intestinal surgery; hernias.

EMILE HOLMAN and LEO ELOESSER. Thoracic surgery.

F. REICHERT and E. TOWNE. Neurosurgical operations.

R. GILMAN, EMMET RIXFORD, EMILE HOLMAN. Thyroid, biliary tract, liver and pancreas surgery.

A. L. FISHER, D. KING and M. MENSOR. Orthopedic operations.

J. DILLON and L. REYNOLDS. Urological operations.

L. EMGE, H. A. STEPHENSON, C. FLEUHMANN, P. E. HOFFMAN, G. CRAIG and W. STEVENS. Gynecological and obstetrical operations.

F. REICHERT and EMILE HOLMAN. Cardiac conditions, circulatory diseases.

C. B. PALMER and R. BURROWS. Injections, anesthesia.

R. A. SCARBOROUGH. Proctological operations.

A. DAVIS and S. BUNNELL. Plastic surgery; industrial cases; skin diseases.

MOUNT ZION HOSPITAL

HAROLD BRUNN. Total thyroidectomy for cardiac disease.

F. I. HARRIS. Torek operation for undescended testicle, first and second stage procedures; resection for lesions of descending colon; radical mastectomy, Percy cautery and endotherm.

A. L. BROWN. Plastic repair of pendulous breasts; herniotomy.

W. WALDEYER. Appendectomy.

M. GROPER and A. WHITE. Blood transfusion, citrate, Linderman and Unger methods.

L. HOFFMAN. Hysterectomy.

L. D. PRINCE, A. SIRBU and DAVID CHARMAK. Radical clavectomy; fracture of os calcis.

H. BLACKFIELD. Plastic correction of congenitally protruding ears.

HAROLD BRUNN and A. L. BROWN. Phrenic avulsion; thoracoplasty.

A. ZOBEL and D. A. SUSNOW. Electrocoagulation of tumors of the rectum; hemorrhoidectomy under local infiltration.

L. C. JACOBS. Calculi of the urinary bladder; transurethral prostatectomy.

H. A. R. KREUTZMANN. The problem of urinary lithiasis; nephrotomy; pyelotomy; nephrectomy.

B. STRAUSS and M. POLSE. Hydrocele operation; plastic operation for phimosis; cystoscopy.

A. EPSTEEN. Injection of vas deferens for chronic epididymitis.

R. K. SMITH. Classical cesarean section.

A. BERNSTEIN. Demonstration of cervical repair immediately following delivery.

F. PEARL. Muscle splitting extraperitoneal lumbar sympathetic ganglionectomy, a new approach; muscle splitting posterior cervicodorsal sympathetic ganglionectomy.

EDWARD H. BOLZE, HERBERT H. SCHULTZ and DR. LAZAR. Demonstration of introduction of anesthesia by avertin, evipal, gas and oxygen, spinal.

ST. MARY'S HOSPITAL

T. E. Bailly. Gastric surgery; gastrectomy.
Rodney Yoell. Gall-bladder surgery; cholecystectomy.
D. Sooy. Surgical intervention for duodenal ulcer.
C. P. Mathe. Nephropexy for nephroptosis.
E. Topham. Inguinal hernia.
Justin McCarthy. Industrial emergency cases.
Edmund Butler. Surgery of the colon.
George K. Rhodes. Emergency surgery.
Edmund Morrissey. Sympathectomy for Raynaud's disease.
Philip Arnot. Obstetrical surgery.
T. Gibson. Nephrectomy.
W. Faulkner. Bronchoscopic diagnosis of lung abscess.
J. Loutzenheiser. Orr treatment for delayed bony union.

LETTERMAN GENERAL HOSPITAL

R. F. Metcalfe. Cauterization of cervix; perineorrhaphy; suspension of uterus; gastrojejunostomy; cholecystectomy; hemorrhoidectomy; colostomy for rectal carcinoma; cesarean section.
F. L. Cole. Hernia; appendectomy; inguinal hernia; ventral hernia.
H. S. Blesse. Genito-urinary operations; electrical resection.
B. S. Burnet. Thoracotomy for empyema; orthopedic operations; bone graft; open reduction of tibia; excision of cartilage, knee.
P. E. Duggins. Curettage and insertion of Carsten pessary for sterility.

ST. JOSEPH'S HOSPITAL

Alson R. Kilgore, J. M. Meherin, F. Sheehy and C. E. Smith. General surgical operations.
R. Soto-Hall and K. Haldeman. Orthopedic operations.
E. Morrissey. Neurosurgical operations.
H. Von Geldern. Gynecological operations.
T. Gibson. Urological operations.

FRENCH HOSPITAL

F. A. Lowe. Fractured humerus; internal derangements of knee joint.
G. W. Pierce and G. O'Connor. Removal of nasal hump.

MARY'S HELP HOSPITAL

R. Millzner. Radical neck dissection.
E. Carlson and C. C. McCrae. Abdominal operations.
M. Mensor and L. Parker. Orthopedic surgery.
M. Vecki. Urological operations.
H. Von Geldern and A. Schmidt. Gynecological and obstetrical operations.

HOSPITAL FOR CHILDREN

C. Hoag. Thyroidectomy.
Muriel E. Edwards. Thyroglossal duct cyst.
Alma Pennington. Supravaginal hysterectomy; total hysterectomy; vaginal plastic.

VETERANS ADMINISTRATION

Staff. Coffey operation for carcinoma of the rectosigmoid, second state; gastrectomy.

SOUTHERN PACIFIC HOSPITAL

W. B. Coffey and J. D. Humber. Superior cervical sympathectomy for angina pectoris, moving picture demonstration in natural color.
C. Mathe and T. Gibson. Transurethral prostatectomy.
E. Greenwood. Cholecystectomy.
F. R. Girard. Inguinal hernia; ambulant treatment by injection.
C. Walker and J. Bohm. Open reduction of fractures.
Oscar F. Nolan and Thomas E. Gibson. Suprapubic prostatectomy.
W. W. Washburn. Thyroid surgery.

ST. LUKE'S HOSPITAL

Alanson Weeks, G. D. Delprat, Paul Castelhun, A. H. Rosburg, Otto H. Pflueger, Dr. Sullivan, Dr. Moore and Albert M. Vollmer. General surgical operations.
George J. McChesney, Rudolph L. Dresel and Dr. Cox. Orthopedic operations.
L. P. Player, Herbert D. Crall and Miley B. Wesson. Urological operations.
J. M. Morgan. Proctological operations.

U. S. MARINE HOSPITAL

Robert A. Jones. Excision of pilonidal sinus and rectal operation; cholecystectomy and autoplasty (Gillies tubular flap); Dupuytren's contracture.
Richey L. Waugh. Inguinal hernioplasty using pedicled fascial strips; operation for sciatica (Heyman); arthrotomy of the knee with excision of internal semilunar cartilage; bunion operation (Peabody); phrenic neurectomy.
Fletcher C. Stewart. Transurethral resection of prostate.

ST. FRANCIS HOSPITAL

G. B. O'Connor. Plastic surgery: Reconstruction of face after burns; rib cartilage transplant to the nose; removal of nasal hump; cleft palate; reconstruction surgery of the hand.
W. W. Washburn. Thyroidectomy.
L. R. Reynolds and O. Nolan. Prostatectomy, ureteral transplants.

SHRINERS' HOSPITAL

Sylvan L. Haas. Longitudinal osteotomy; transplantation of muscles in paralysis; stabilization of foot; fusion of spine; lengthening of leg; congenital dislocation of hip; Sever operation for obstetrical paralysis with transplantation of teres major; fusion of hip; plastic operation.

FRANKLIN HOSPITAL

E. Gehrels. Gastro-intestinal surgery.
L. Brooks. Abdominal operations.
J. Sale, V. Dillon, W. Montgomery and W. Cox. Industrial surgery and orthopedics.
G. W. Pierce and G. O'Connor. Reconstruction surgery of hand, face and neck after burns; repair of eyelids; correction of flexion contractures.

CLINICAL DEMONSTRATIONS IN SAN FRANCISCO HOSPITALS—DAILY

GENERAL SURGERY

A. S. WHITE and F. I. HARRIS. Injection treatment of hernia.
HAROLD BRUNN. Appendicitis.
S. R. SHERMAN. Rupture of the spleen.
J. HOMER WOOLSEY and H. GLENN BELL. Splenectomy.
WALTER B. COFFEY. Inspection of an industrial medical and surgical center; ward rounds; demonstration of cases; postoperative treatment.
EMMET RIXFORD. Knotty problems in industrial surgery: Traumatic carcinoma of breast; ruptured heart; traumatic thrombosis of iliac and other large veins.
EMILE HOLMAN. Operative cure of recurrent and direct inguinal hernia.
GEORGE K. RHODES. Hematogenous perinephric abscess; peritonitis and drainage.
M. W. DEBENHAM. Aseptic meningitis following spinal anesthesia.
A. L. BROWN. Pulmonary embolectomy, motion picture demonstration of the Trendelenburg operation on cadaver.
H. BRODIE STEPHENS. Subphrenic abscess; vaccination of the pleural and abdominal cavities.
WALTER BIRNBAUM. Tendon repair; acute gonococcic tenosynovitis.
ALSON R. KILGORE, OTTO H. PFLUEGER and R. S. STONE. Treatment of breast cancer, end results.
OTTO H. PFLUEGER. Soft tissue sarcomas.
ALSON R. KILGORE. Cystic disease of the breast; cancer.
C. L. CALLANDER. Gas bacillus infection; new amputation of thigh in lower third; treatment of septic joints.
EDMUND BUTLER. Emergency surgery.
EDMUND BUTLER, L. R. REYNOLDS, L. H. GARLAND and J. B. MCNAUGHT. Old healed ruptured bladders, diagnostic difficulties and value of X-ray in diagnosis; X-ray in differential diagnosis of acute abdomen.
EUGENE S. KILGORE. Circulatory disease in differential diagnosis of acute abdomen.
CARLETON MATHEWSON, JR. and J. B. MCNAUGHT. Lymphogranuloma inguinale.
A. S. MUSANTE. Postoperative infections.
I. W. THORNE. Squamous and basal cell carcinoma of face and neck, pathology, diagnosis and treatment.
Z. E. BOLIN. Biopsies and tumor surgery; mixed tumors of the parotid.
EVERETT CARLSON. Carotid body tumors; splenectomy, indications and technique.
FRANK E. STILES. Treatment of varicose veins.
J. F. RICKARD. Intestinal obstruction.

SURGERY OF THE THYROID

WILLIAM J. KERR, HENRY H. SEARLS, JANE T. PAXSON and R. S. STONE. Activities of the thyroid committee of the University of California Hospital with follow-up studies after various lines of treatment.
HENRY H. SEARLS, E. I. BARTLETT and C. L. CONNOR. Chronic diffuse thyroiditis.
HENRY H. SEARLS and JANE T. PAXSON. Clinical picture of toxic adenoma with normal or lowered metabolic rate.
WILLIAM J. KERR. The heart in parathyroidism.
M. L. MONTGOMERY. Lingual thyroid.
THEODORE ALTHAUSEN. Surgical implications of hepatic damage in thyrotoxicosis.
R. J. MILLZNER. Parathyroid damage during thyroidectomy.

GENITO-URINARY SURGERY

FRANK HINMAN, CLARK M. JOHNSON and BRENT WEYMAN. Tumors of the testicle, pathology, demonstration of hormone tests, end-results; uretero-intestinal anastomosis, experimental work, drawings and motion picture demonstration, demonstration of patients; prostatism, pathology, indications for different types of surgery end-results by different methods.
C. P. MATHE. Surgery of the prostate.
T. E. GIBSON. Newer aspects of renal tuberculosis.
L. P. PLAYER and H. D. CRALL. Gracilis transplantation for urinary incontinence.
MILEY B. WESSON. Conservative surgical treatment of nephrolithiasis.
L. C. JACOBS. Calculi of urinary bladder; suprapubic and transurethral prostatectomy.
H. A. R. KREUTZMANN. Urinary lithiasis, nephrotomy, pyelotomy and nephrectomy.
BERNARD STRAUSS and M. L. POLSE. Operation for hydrocele; plastic operation for phimosis.
A. EPSTEEN. Injection of vas deferens for chronic epididymitis.
J. V. LEONARD and GEORGE W. HARTMAN. Demonstration in urology.
C. P. MATHE and T. E. GIBSON. Transurethral prostatectomy.
T. E. GIBSON and O. F. NOLAN. Suprapubic prostatectomy.
J. R. DILLON. Treatment of chronic pyelitis and pyelonephritis; treatment of cancer of prostate; technical improvements in surgical treatment of undescended testicle.
W. E. STEVENS. Unusual pathological conditions of the urinary tract in women.
EDGAR POTH. A new aseptic technique for uretero-enterostomy; mechanism of ascending infection of the urinary tract; experimental observations.
SIDNEY OLSEN. Tuberculosis of the genito-urinary tract; urinary calculi.
CLARK M. JOHNSON. Trauma of the genito-urinary tract; infections of the genito-urinary tract; renal and pararenal infections; renal anomalies.
L. P. PLAYER. Kidney lavage.
W. A. CARROLL. Ureteral lithiasis; rupture of kidney.
T. O. POWELL. Newer knowledge of tumors of the testicle with special reference to gonadotropic hormone excreted in the urine.
M. R. OTTINGER, LLOYD R. REYNOLDS and J. B. MCNAUGHT. Torek operation of undescended testicle; torsion of testicle.
GEORGE W. HARTMAN. Hematuria and pyuria; renal tuberculosis.
W. A. SUMNER. Relationship of chronic infections to lesions of the genito-urinary tract.
LEWIS MICHELSON. Obstruction of the neck of the bladder in the female.
R. GLENN CRAIG. Ureteral pain of obscure origin.
MORRELL VECKI. Renal movability.

SURGERY OF INFECTIONS

A. S. WHITE. Treatment of staphylococcus infections with staphloid.
S. A. GOLDMAN. Studies on staphylococcus infections.
F. J. MCCARTHY. End-results in infections of the hand.
B. F. ALDEN. Relation of focal infection to Wassermann-fast lues.

ORTHOPEDIC SURGERY

GEORGE J. MCCHESNEY, W. COX and R. L. DRESEL. Fracture of neck of femur; treatment without external splinting.

L. D. PRINCE, A. B. SIRBU and D. D. CHARMACK. Fractures of os calcis; replacement of tibial shaft by fibula following osteomyelitis; treatment of bursitis.

R. L. WAUGH. Clinical demonstration of Roger Anderson "Ought-O-Matic" splint and skeletal traction and countertraction methods applicable to Thomas or Hodgen splints.

LEROY C. ABBOTT. The shoulder joint.

JOHN B. DE C. M. SAUNDERS. The shoulder joint.

J. F. RINEHART. Vitamin C deficiency in arthritis.

KEENE HALDEMAN and JOHN B. DE C. M. SAUNDERS. Demonstrations of bone growth.

FRANCES BAKER. Heat therapy.

F. A. LOWE. Internal derangements of knee joint, clinic and motion picture demonstration; fracture of humerus, clinic and motion picture of demonstration.

J. J. LOUTZENHEISER. Arthrodesis of foot.

S. L. HAAS. Application of Hibbs-Risser plaster for scoliosis; results of treatment for scoliosis; results of tendon transplantation; Leggs-Perthes disease.

J. J. SALE, W. O. MONTGOMERY, V. M. DILLON and W. J. COX. Industrial surgery and orthopedics.

J. H. O'CONNOR. Reduction of complicated fractures, closed methods, demonstration of cases, indications for open reduction.

C. A. WALKER. End-results of open reduction of fractures; treatment of compression fractures of spine, 250 cases; fractures of clavicle and patella.

W. W. WASHBURN. Disabilities following fractures, factors influencing period of recovery.

LEONARD W. ELY. Arthritis of the hip.

D. KING. Functional anatomy and pathology of the shoulder joint.

A. L. FISHER. Treatment of flat feet.

MERRILL C. MENSOR. Osteogenic sarcoma of spine; relation of bacteriophage to the Orr treatment of osteomyelitis.

NELSON J. HOWARD. Traumatic lesions of bursæ, tendons and muscles.

LEON PARKER. Familial tendencies in Paget's disease.

D. KING. Treatment of chronic sclerosing osteomyelitis.

F. G. LINDE. Compression fractures of spine; non-union of fractures.

F. C. BOST. Hibbs-Risser treatment of scoliosis; dislocation of carpal semilunar; fracture of ankle; ligamentous tears of ankle; treatment of fracture of os calcis.

W. J. COX. Internal derangement of knee joint, rupture of ligaments; treatment of fracture of femoral neck with Smith-Peterson nails.

KEENE O. HALDEMAN. Pathology of acute osteomyelitis; pathology of chronic infections of bone.

RALPH SOTO-HALL and KEENE O. HALDEMAN. Fracture dislocation of cervical spine; Duncan's traction apparatus.

PAUL E. JOHNSON, B. H. HENNING and JOHN A. KENNEDY. Disability ratings of Veterans Administration for orthopedic conditions of the extremities.

CARLETON MATHEWSON, JR. and J. B. MCNAUGHT. Treatment of spiral fractures of tibia; open and closed methods of treatment of fractures of extremities; tuberculosis of pelvis.

D. KING, J. M. MEHERIN and R. A. SCARBOROUGH. Fracture of carpal scaphoid; surgical approaches to bones and joints; Orr method of treatment of osteomyelitis.

NELSON J. HOWARD. Fractures of the upper end of the humerus, motion picture demonstration.

MERRILL C. MENSOR and LEON PARKER. Unusual fractures of the spine; treatment of osteomyelitis with surgical maggots.

C. C. MCRAE. Injuries of small bones of the hand.

EDGAR L. GILCREEST. Problems in treatment of fractures.

THORACIC SURGERY

HAROLD BRUNN, A. L. BROWN, H. ROSENBLUM and J. J. SAMPSON. Symposium on surgery of the heart with particular reference to adhesive pericarditis.

LEO ELOESSER, PHILIP H. PIERSON, W. L. ROGERS, W. G. BURKHARD, DAVID A. WOOD, W. R. CLARK and L. H. GARLAND. Various types of bronchial stenosis; mycotic infections of the lung; tumors of the lung; empyema.

EMILE HOLMAN. Technical improvements in partial selective thoracoplasty; resection of transverse process; resection of scapula; ligation of the pulmonary artery as a therapeutic measure in pulmonary hemorrhage; carcinoma of lung simulating inflammatory disease.

HAROLD BRUNN, SIDNEY J. SHIPMAN, H. BRODIE STEPHENS, A. L. BROWN, M. W. DEBENHAM and A. GOLDMAN. Lung suppurations; empyema; artificial pneumothorax; phrenic avulsion; thoracoplasty.

ALANSON WEEKS and G. D. DELPRAT. Thoracoplasty.

RAY KISTLER. Diaphragmatic hernia.

SIDNEY J. SHIPMAN. Pneumothorax in pneumonia.

W. B. FAULKNER, JR. Bronchiectasis; treatment of chest injuries.

A. L. BROWN. Collapse therapy in pulmonary tuberculosis.

S. SHERMAN. Lymphoblastoma of mediastinum.

C. A. WALKER. Phrenicectomy for pleuropericardial adhesions.

A. GOLDMAN. Staphylococcic infections of the lung; chemotherapy in tuberculosis.

T. F. MULLEN. Antethoracic esophagoplasty.

MARY E. MATHES. Experimental study of the effect of various pathological conditions upon the dual blood supply of the lungs.

EDGAR POTH. A simple apparatus for tidal and siphon irrigation and its application in treatment of empyema.

DAVID A. WOOD and MARY E. MATHES. Exhibit of clinical and experimental observations on the dual blood supply of the lungs in various pathological states.

NEUROSURGERY

HOWARD C. NAFFZIGER. Late results in the treatment of malignant exophthalmos; brain tumors; factors influencing recovery after peripheral nerve injury; cervical ribs and "the scalenus syndrome without cervical ribs."

HOWARD W. FLEMING. Subdural hematomata; cerebrospinal rhinorrhea; relief of intractable pain; cranial approach for orbital tumors; craniocerebral injuries.

EDMUND MORRISSEY. Neurologic clinic on lesions of the cauda equina; diagnosis and treatment of subdural hemorrhage; diagnosis of subdural hemorrhage.

O. W. JONES, JR. Spinal cord tumors.

H. A. BROWN. Low back injuries; spinal cord injuries.

E. B. TOWNE. Treatment of acute head injuries.

F. L. REICHERT. Neuralgias of cranial nerves, demonstration of patient and lantern slides.

ROBERT AIRD. Encephalography, clinical and experimental; intradural alcohol injections for intractable pain.

E. B. TOWNE, E. MORRISSEY, J. W. WOLFSOHN and D. WOOD. Surgical lesions of the spinal cord; dynamics of epilepsy.

L. B. LAWRENCE. Spinal cord tumors; tumors of cauda equina.

LEE HAND. Regeneration of peripheral nerves of hand.

GYNECOLOGY AND OBSTETRICS

WILLIAM G. MOORE. Endometriosis; fibromyomata of uterus.

A. M. VOLLMER. Rubin's insufflation test; trichomonas vaginalis.

R. K. SMITH. Classical cesarean section, motion picture demonstration.

FRANK LYNCH, ALICE MAXWELL and R. S. STONE. Uterine cancer, follow-up, X-ray therapy, radium therapy.

MARGARET SCHULZE. Special ovarian tumors.

A. H. HEALD and ALICE MAXWELL. X-ray pelvimetry, direct method.

PHILIP H. ARNOT. Conduct of labor in posterior postion.

LUDWIG EMGE. Dysmenorrhea, causes and treatment; sterility, diagnosis and treatment.

C. F. FLUHMANN, P. E. HOFFMAN and GERTRUDE F. JONES. Endocrinological aspects of gynecology, modern methods of diagnosis, blood and urine hormone tests, biopsy of endometrium, hormone therapy.

A. V. PETTIT. Results of hyperpyrexia in treatment of acute and chronic pelvic inflammatory disease.

LUDWIG EMGE. Radiation therapy of carcinoma of cervix, methods and end-results.

A. M. VOLLMER. Treatment of abortions.

MARGARET SCHULZE. Multiple pregnancies; pyelitis with pregnancy; hydatidiform mole and chorio-epithelioma; cardiac disease with pregnancy.

KARL L. SCHAUPP. Fibromyoma of the uterus.

HANS VON GELDERN. Plastic operations on pelvis.

C. L. COOLEY. Demonstration of gynecological cases.

R. D. DUNN. Treatment of incomplete abortions.

D. A. DALLAS. Operations in obstetrics.

BEVERLY SIMPSON. Separated placenta.

ADOLPH E. SCHMIDT. Uterine bleeding.

SURGERY OF THE GASTRO-INTESTINAL TRACT

HAROLD BRUNN. Cancer of the rectum.

F. I. HARRIS. Cicatrizing (chronic) enteritis (regional ileitis); treatment of appendix stump, noninversion.

FRED H. KRUSE. The more common complications of peptic ulcer.

E. J. BEST, F. H. KRUSE, THEODORE ALTHAUSEN and RALPH RABINOWITZ. Postoperative care of intestinal conditions.

M. F. CUNHA. Primary duodenitis; end-results of ulcer cases, types of operation, causes of recurrence.

LEON GOLDMAN and THEODORE ALTHAUSEN. Pseudo perforation of peptic ulcer.

J. HOMER WOOLSEY and H. GLENN BELL. Carcinoma of stomach.

M. L. MONTGOMERY and JOSEPH M. SWINDT. Acute intestinal obstruction, experimental and clinical.

H. GLENN BELL. Subacute intestinal obstruction, localized type (chronic cicatrizing enteritis).

H. GLENN BELL and LEON GOLDMAN. Congenital lesions, tumors, diverticula of small bowel.

M. S. WOOLF, LEON GOLDMAN and H. GLENN BELL. Carcinoma of large bowel.

DUDLEY SMITH and J. W. MORGAN. Carcinoma of rectum.

ASA W. COLLINS. Pylorectomy and gastro-enterostomy.

LEROY BROOKS. Diagnosis and treatment of intestinal obstruction.

P. K. BROWN. Peptic ulcer, indications for surgical treatment.

W. W. WASHBURN. Acute perforation of peptic ulcer, complications and end-results in 100 cases.

ERNST GEHRELS. Radical surgery for gastric and duodenal ulcers; diverticulitis of colon; closure of colostomy; preservation of anal sphincter.

J. A. GUILFOIL. Chronic appendicitis, end-results of operation.

J. E. BOHM. Mortality rate of operations for appendicitis.

R. A. SCARBOROUGH. Developments in surgical treatment of carcinoma of rectum, 200 cases.

EMILE HOLMAN. Causes for failure to control symptoms and to prevent gastrojejunal ulcer in gastric surgery.

GUNTHER W. NAGEL, F. L. REICHERT and MARY E. MATHES. Chronic regional enteritis, clinical, experimental.

DAVID A. WOOD. Multiple primary carcinomata of colon complicating multiple polyposis of colon.

NELSON J. HOWARD. Amebic granuloma of large bowel.

HAROLD BRUNN. Carcinoma of large bowel; carcinoma of rectum; bowel obstruction.

GEORGE K. RHODES. Spontaneous perforation of cecum from obstruction in distal colon.

DANIEL SOOY. Choice of operation in gastric surgery.

EDWARD TOPHAM. End-results in surgery for gastric ulcer.

H. P. HILL, GEORGE BARNETT, J. M. MEHERIN, J. W. CLINE, JR., CARLETON MATHEWSON, JR., J. B. MCNAUGHT and A. C. MCKENNEY. Lesions of the upper gastro-intestinal tract; amebic infections of liver and gastro-intestinal tract.

DUDLEY SMITH. Operation for rectal fistula and hemorrhoidectomy, motion picture demonstration.

SURGERY OF THE BILIARY TRACT, LIVER AND PANCREAS

ALANSON WEEKS and G. D. DELPRAT. Common duct stone; hydatid disease of liver; granuloma inguinale.

F. I. HARRIS. Acute cholecystitis.

CARL HOAG. Reconstruction of common duct.

H. CLARE SHEPARDSON and HANS LISSER. Pancreatic dysfunction; hypoglycemia.

H. GLENN BELL and THEODORE ALTHAUSEN. Operative mortality and pre-operative management of cholecystitis, glucose therapy, Rose-Bengal and other tests.

FRED H. KRUSE and THEODORE ALTHAUSEN. Medical and surgical jaundice; cirrhosis of liver, differential diagnosis from carcinoma of stomach.

JESSE L. CARR and FREDERICK S. FOOTE. Experimental work in human jaundice.

KARL SCHMIDT. The bile salts.

EMILE HOLMAN. Postoperative and inflammatory stenosis of the bile passages.

M. W. DEBENHAM and J. M. SWINDT. Liver abscess.

STANLEY H. MENTZER. Acute cholecystitis; obstructive cholecystitis.

RODNEY A. YOELL. Gall-bladder anomalies.

T. F. MULLEN. Recurrence of symptoms after biliary tract surgery.

ENDOCRINOLOGY

R. F. ESCAMILLA. Abdominal pain of endocrine origin.

SAMUEL COHN and F. I. HARRIS. Treatment of undescended testicle by operation and glandular extracts.

LEO STANLEY. Endocrinology in a penal institution.

CIRCULATORY DISEASE

M. L. MONTGOMERY. Therapeutic venous occlusion.

C. A. NOBLE, JR. Postoperative cardiac versus circulatory collapse.

CLINICS IN ALAMEDA COUNTY HOSPITALS—WEDNESDAY

ALAMEDA COUNTY HOSPITAL

WHITFIELD CRANE and W. EARL MITCHELL—9. Carcinoma of stomach.

FRANK H. BOWLES and THEODORE LAWSON—10. Carcinoma of cecum.

H. W. HARDING and DON D. WEAVER—11. Carcinoma of colon.

LEMUEL P. ADAMS—12. Carcinoma of breast.

SUMNER EVERINGHAM—9. Extrapleural thoracoplasty; intrapleural pneumolysis; clinic on phrenic interruption and thoracoplasty. Discussion by CHESLEY BUSH.

WARREN B. ALLEN—12. Neurosurgery.

W. F. HOLCOMB—9. Arthroplasty of hip.

L. B. BARNARD—10. Arthroplasty of shoulder.

E. N. EWER—9. Total hysterectomy; subtotal hysterectomy; discussion of obstetrical service at Alameda County Hospital.

CLARENCE A. DEPUY—11. Gynecological cancer clinic. Demonstration of intraspinal alcohol injection and presentation of cases.

ALBERT M. MEADS, LLOYD KINDALL, JOHN A. DAUGHERTY, T. I. BUCKLEY and associates—9. Perineal prostatectomy, suprapubic prostatectomy, resectoscopic prostatectomy. Operations, demonstration of cases and discussion.

Dry Clinics, 2—4:30

CHARLES A. DUKES and associates. Cancer clinic.

HAROLD H. HITCHCOCK, N. A. CARY and associates. Traumatic and orthopedic clinic; demonstration of Sweetland cast dryer, Bell table, plaster models, splints, etc.

W. H. SARGENT and C. B. BOWEN. X-ray exhibit and discussion.

GERTRUDE MOORE. Pathological exhibit and conference.

BERKELEY GENERAL HOSPITAL

Dry Clinics, 9—12

FRANK D. WALSH. Cholecystitis, observations and comments on surgical treatment.

CLAUDE H. CHURCH. Ectopic pregnancy recurring on same side.

WILLIAM W. CROSS. Polycystic kidney; nephrolithiasis; prostatic management.

J. F. CARLSON. Osteochondromatosis involving all epiphyses in one extremity; clavicle dressings.

W. W. REICH. Parathyroid disease, gross specimens and microprojections.

R. G. VAN NUYS. X-ray demonstration and discussion.

CHILDREN'S HOSPITAL

ROY NELSON—9. Demonstration of methods of treatment of esophageal stricture due to lye.

W. W. CROSS—9. Postmortem findings in the kidneys of children, lantern slide demonstration.

CLIFFORD SWEET—9. Clinic on undescended testes: Demonstration of postoperative results; discussion of the effect of antuitrin S; demonstration of operation.

ALTA BATES HOSPITAL

Staff—9. Operations and dry clinics.

SAMUEL MERRITT HOSPITAL

WARREN B. ALLEN—9. Reconstruction of skull defects, operation and demonstration of cases.

W. F. HOLCOMB and D. D. TOFFLEMEIR—9. Orthopedic operations and demonstrations.

MARK L. EMERSON—9. Rectal surgery and presentation of cases.

FRANK H. BOWLES—9. Thyroidectomy.

W. H. SARGENT—9. X-ray demonstration and discussion of cases.

ROBERT A. GLENN—9. Pathological exhibit; demonstration of frozen section technique and specimens.

WHITFIELD CRANE—10:30. Peptic ulcer; Judd pyloroplasty.

W. EARL MITCHELL—10:30. Pelvic tumor.

HENNING KOFORD—10:30. Cholecystectomy.

CHARLES A. DUKES—11. Apicolysis, operation; demonstration of thoracic cases. Discussion by HAROLD TRIMBLE.

H. N. ROWELL, A. M. SMITH, W. H. STRIETMANN, A. A. ALEXANDER, W. S. KUDER, STEWART V. IRWIN, H. GORDON MACLEAN, FLETCHER B. TAYLOR, VERNE G. ALDERSON, and HOBART ROBERTS—2. Symposium on pre- and postoperative care: Management of surgical jaundice and stomach cases; diabetes in surgery; traumatic and postoperative pneumonia; cardiac and renal complications; postoperative psychosis; allergy in relation to abdominal surgery; discussion and demonstration of cases.

PERALTA HOSPITAL

J. L. LOHSE—9. Cholecystectomy.

ERGO A. MAJORS—9. Carcinoma of breast, radical removal.

F. M. LOOMIS and JOHN W. SHERRICK—9. Porro cesarean section.

CHARLES B. FOWLER—9. Orthopedic treatment of spondylolisthesis; correction of upper extremity involvement in poliomyelitis.

H. J. TEMPLETON and J. LUNSFORD—10. Electric desiccation in cutaneous malignancies.

JOHN W. SHERRICK—10. Vaginal plastic.

T. FLOYD BELL—10. Pelvic tumor.

T. C. LAWSON—11. Hernia, fascial repair.

P. N. JACOBSEN—11. Bladder surgery.

PAUL MICHAEL—9 to 1. Pathological demonstration and exhibit.

J. D. COATES—9 to 1. X-ray demonstration and exhibit.

COWELL MEMORIAL HOSPITAL

HERBERT EVANS, ROBERT LEGGE, C. A. KOFOID and associates—9. Exhibit and discussion of latest advances in endocrinology; inspection of laboratories and hospital with special reference to the systematic medical care of university students; discussion of laboratory technique with particular reference to amebiasis.

ALAMEDA SANATORIUM

J. OHANNESON—9. Hernioplasty under local anesthesia; appendectomy.

G. R. BURKE—9. Cholecystectomy.

CHANNING HALL—10. Resection of stomach.

PROVIDENCE HOSPITAL

O. D. HAMLIN—9. Intestinal anastomosis.
J. RADFORD FEARN—9. Vaginal hysterectomy under local anesthesia.
A. REIS—10. Cholecystectomy, new method.
THEODORE M. WELLER—10. Cesarean section.
N. AUSTIN CARY—11. Sacro-iliac fusion.
PHILIP J. DICK—11. Posterior gastro-enterostomy.
MICHAEL TORRANO—12. Herniotomy under local anesthesia.
S. A. JELTE—9 to 12. X-ray demonstration and discussion.

EAST OAKLAND HOSPITAL

DON D. WEAVER—9. Ulcer of the stomach.
O. R. ETTER—9. Surgery in the diabetic patient, dry clinic.
R. G. VAN NUYS—10. Dry clinic: Visceroptosis and position of the viscera in healthy young adults; X-ray demonstration.
BROOKS STEPHENS—10:30. Hallux valgus.
CLAIR RASOR—10:30. Prolapse of uterus.
ALEXANDER H. GRIFFITH—11. Carcinoma at the recto-sigmoidal juncture, Lahey technique.

SURGERY OF THE EYE, EAR, NOSE, AND THROAT

CLINICS IN SAN FRANCISCO HOSPITALS—DAILY

UNIVERSITY OF CALIFORNIA HOSPITAL

Tuesday

JOSEPH L. MCCOOL, FREDERICK C. CORDES, JOSEPH W. CRAWFORD, C. ALLEN DICKEY and DAVID O. HARRINGTON—9. Ophthalmological operations.
R. C. MARTIN and FREDERICK C. CORDES—9. Toti-Mosher operation.
WALLACE SMITH, LOUIS MORRISON and EDITH STOKER—9. Otolaryngological operations.

Dry Clinics—2

FREDERICK C. CORDES. Surgery of traumatic cataracts.
J. W. CRAWFORD. Tuberculosis of the eye.
C. ALLEN DICKEY. Surgery of the vertical muscles.
DAVID HARRINGTON. Contact glasses, practical demonstration.
R. C. MARTIN and STERLING BUNNELL. Injuries and repair of the facial nerve.

Thursday

JOSEPH L. MCCOOL, FREDERICK C. CORDES, JOSEPH W. CRAWFORD, C. ALLEN DICKEY and DAVID O. HARRINGTON—9. Ophthalmological operations.
R. C. MARTIN and FREDERICK C. CORDES—9. Toti-Mosher operation.
WALLACE SMITH, LOUIS MORRISON and EDITH STOKER—9. Otolaryngological operations.

Dry Clinics—2

JOHN SAUNDERS. Regional anatomy of the mastoid and pathways of infection of the intracranium.
HOWARD C. NAFFZIGER. Brain abscess arising from middle ear and mastoid infections.
WALLACE SMITH. Phlebitis and thrombosis following middle ear and mastoid infections.

Friday—2

FREDERICK C. CORDES. Surgery of complicated cataracts.
J. W. CRAWFORD. The eye in diabetes.
C. ALLEN DICKEY. The value of orthoptic treatment.
DAVID HARRINGTON. Tobacco amblyopia and its treatment.

ST. MARY'S HOSPITAL

Thursday—2

FRANCIS CONLAN, STANLEY BURNS and FRANK HAND. Treatment of posterior sinusitis. Blood dyscrasias in relation to the ear, nose and throat. Treatment of bilateral abductor paralysis.
FRANK HAND. Radical antrum.

SAN FRANCISCO HOSPITAL

Tuesday—2

WARREN D. HORNER. External iridectomy; history, uses, technique and advantages.
C. ALLEN DICKEY and J. W. CRAWFORD. Safety procedures in cataract operations; akinesis, intra-orbital injections, lid sutures, pre-operative medication.
WARREN D. HORNER, C. ALLEN DICKEY and J. W. CRAWFORD. The use of synthetic epinephrin bitartrate in ocular therapeutics.
AUBREY RAWLINS. Osteoma of the antrum; some curious foreign bodies in the lungs; cases of recovery from otitic meningitis; extensive osteomyelitis of the frontal bone.
HARRINGTON B. GRAHAM. Foreign bodies in the lungs; stenosis of the esophagus; cancer of the larynx.
HARRINGTON B. GRAHAM and J. M. WOLFSOHN. Extensive abscess of the meninges.
RAE ASHLEY. Treatment of tuberculosis of the larynx.

HOSPITAL FOR CHILDREN

Thursday—2

GEORGE N. HOSFORD and AVERY M. HICKS. Technique for the determination of the hydrogen ion concentration of tears. The significance of pH of tears in ocular symptoms and treatment. Indications for and results of orthoptic training. Relation of vertical imbalance of extra-ocular muscles to gastric symptoms, posture, temperament and aptitude for school work and occupation. Congenital muscle palsy. Motion picture demonstration of O'Connor technique for heterophoria and heterotropia.

Days to be Announced

GEORGE N. HOSFORD and AVERY M. HICKS—9. Extraction of congenital cataract; muscle operations, O'Connor cinch shortening for simple exotropia, simple esotropia, vertical deviations; muscle transplants for external rectus palsy, superior rectus for paralysis of the superior oblique (Jackson's technique), Motais' operation for congenital ptosis; Toti-Mosher operation for occlusion of nasolacrymal duct (with Drs. Martin and Hosmer).

STANFORD UNIVERSITY SCHOOL OF MEDICINE

Wednesday—2

FRANK RODIN. Congenital and hereditary eye defects.
AVERY HICKS. Ocular torticolis.
DOHRMANN PISCHEL. Retinal detachment, methods and results.

MOUNT ZION HOSPITAL

Tuesday

HERBERT J. COHN, EDWARD LIPSETT and JOHN SKAFF—9. Tonsil operations, local and general anesthesia, dissection, Sluder, snaretome.

Wednesday—2

HERBERT J. COHN, EDWARD LIPSETT and JOHN SKAFF. Symposium on mastoidectomy.
GEORGE S. LACHMAN. Treatment of corneal ulcers.
CHARLES WEISS. Recently developed concepts in immunology and bacteriology of value to the ophthalmologist.
FRANK H. RODIN. Treatment of acute iridocyclitis.
G. Y. RUSK. Pathological demonstration of various eye conditions.

Thursday

Staff—9. Nasal operations: Submucous resection, electrocoagulation of turbinates, sinus surgery.

Days to Be Announced

FRANK H. RODIN and GEORGE S. LACHMAN—9. Ophthalmological operations: Cataract, strabismus, plastic on eyelids.

SOUTHERN PACIFIC HOSPITAL

Thursday—2

WILBUR F. SWEET and JOHN C. WILLIAMS. Clinics and demonstration of cases.

LETTERMAN GENERAL HOSPITAL

Tuesday

A. E. SCHLANSER and HERBERT H. PRICE—9. Tonsillectomies; adenoidectomies, general anesthesia.
HARVEY C. MAXWELL—9:30. Eye surgery, general anesthesia: Strabismus correction by O'Connor tendon cinch and by Jamieson recession.

Wednesday

A. E. SCHLANSER—9. Tonsillectomies, local anesthesia; nasal operations, local anesthesia.

Thursday

HARVEY C. MAXWELL—9. Eye operations, local anesthesia; cataract extraction, pterygium transplant, strabismus correction.

Friday

A. E. SCHLANSER, HERBERT H. PRICE and HARVEY C. MAXWELL—9. Sinus surgery, local anesthesia; extranasal radical frontal ethmosphenoidectomy; radical maxillary sinusotomy; bronchoscopy; esophagoscopy.

ST. LUKE'S HOSPITAL

Tuesday and Thursday

JOSEPH L. MCCOOL, C. ALLEN DICKEY, A. E. EDGERTON and CHARLES BATES—9. Ophthalmological clinic.

VETERANS ADMINISTRATION

Staff. Bronchoscopic examinations.

CLINICS IN ALAMEDA COUNTY HOSPITALS—WEDNESDAY

PROVIDENCE HOSPITAL

A. J. HOWELL—9. Reconstruction of nose.
RODERIC O'CONNOR—9. Muscle shortening; cataract; Curran operation.
GEORGE MCCLURE and NELSON KEELER—9. Ear, nose and throat surgery.
RANDOLPH SHARPSTEEN—9. Motais' operation.
ROY NELSON—9. Esophagoscopy and bronchoscopy.
BRUCE STEPHENS, JR.—10. Cataract operation.
FRANK BAXTER—10. Ear, nose and throat operations.
MILTON H. SHUTES—10. Ear, nose and throat operations.
ALEXANDER GALBRAITH—10. Ear, nose and throat operations.
W. A. MAGRATH—11. Eye operations.
ALVIN P. WOLD—11. Eye surgery.
F. C. KRACAW—11. Ear, nose and throat surgery.
R. J. NUTTING—12. Eye operations.
P. T. LEFTWICH—12. Ear, nose and throat surgery.
FRANCIS SHOOK—12. Ear, nose and throat surgery.
SYDNEY N. PARKINSON—12. Treatment of acute and subacute paranasal sinus infections, lantern slides and motion picture demonstration.

Dry Clinic, 2—4:30 p.m.

Staff. Discussion of operative procedures, demonstration of cases, lantern and motion picture demonstration.

ALAMEDA SANATORIUM

B. M. STEPHENS—11. Cataract.

CHILDREN'S HOSPITAL

M. E. LANDO—10. Strabismus, operative treatment.